PREPARATION, STRUCTURE, AND REACTIVITY OF THE FIRST BICYCLIC BENZIODAZOLE AND ITS MONOCYCLIC ANALOGUE

A THESIS

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DEDICATION

I would like to dedicate this thesis to God, my parents (Anita Sandford-Shea and Kevin Shea), and my friends (Jacob Meyer, Cody Haala, Tom Brumbaugh, Adam Wentz, Sam Betland, Jordan Toole, and Nathan Kovach), for I could not have done this without their continuous support.

Abstract

Nitrogen containing mono-heterocyclic hypervalent iodine(III) compounds, benziodazoles, have been investigated by several research groups as well as ours. These compounds are commonly used as efficient oxidative reagents for various organic substrates. The preparation, structure, and reactivity of the first bicyclic benziodazole compound, *N*,*N*'-diisopropylbenziodazole, will be reported and compared to the monocyclic *N*-isopropyl-*m*-chlorobenzoate benziodazole. Both benziodazoles were prepared by the *m*-chloroperoxybenzoic acid oxidation of 2-iodo-*N*-isopropylbenzamide or 2-iodo-*N,N'*-diisiopropylisophthalamide, respectively, and their structures were established by X-ray crystallography. These benziodazoles were investigated as efficient reagents for oxidatively assisted coupling reactions to form esters and amides.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Symbols and Abbreviations

amu: Atomic mass unit

DIB: (Diacetoxyiodo)benzene

HTIB: Hydroxy(tosyloxy)iodobenzene

IUPAC: The International Union of Pure and Applied Chemistry

IBX: 2-iodoxybenzoic acid

DMP: Dess-Martin periodinane

MeOH: Methanol

Ph: Phenyl

Me: Methyl

m-CPBA: *meta*-chloroperoxybenzoic acid

*i*Pr: Isopropyl

*t*Bu: Tertiary butyl

NMR: Nuclear magnetic resonance

HRMS: High resolution mass spectroscopy

Bn: Benzyl

Pr: Propyl

GCMS: Gas chromatography mass spectrometry

DMAP: 4-dimethylaminopyridine

Py: Pyridine

Et: Ethyl

Et_3N: Triethylamine

TBAI: Tetrabutylammonium iodide

THF: Tetrahydrofuran

DABCO: 1,4-diazabicyclo[2.2.2]octane

*t*BuOK: Potassium tert-butoxide

TMSOTf: Trimethylsilyl trifluoromethanesulfanoate

p-: *para*-

FTIR: Fourier transform infrared

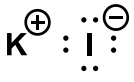
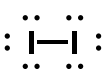
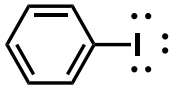
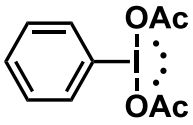
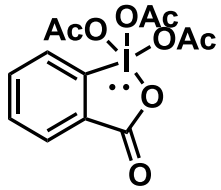
PPh_3: Triphenyl phosphine

Å: Angstrom

1. Introduction

Iodine, the element with atomic number 53, can be found in the seventeenth period of the fourth row on the periodic table. Iodine, with an atomic mass of 126.9 amu, can be considered as the heaviest non-radioactive element among the non-metals. Among the halogens, iodine is the most polarizable and least electronegative. These properties allow iodine to exist in a variety of oxidation states, including -1, 0, +1, +3, +5, and +7.[1] Compounds shown below in Table 1 provide an example of iodine in each of these oxidation states.

Table 1: An example of iodine in each of its oxidation states.

Iodine Reagent						IF_7
Valence Electron Number	8	8	8	10	12	14
Valence	-1	0	+1	+3	+5	+7

Iodine species with oxidation states of +3, +5, and +7 are considered to be hypervalent. That is, the iodine atom has expanded beyond the normal octet of valence electrons. When the iodine atom has an oxidation state of +3, +5, or +7 it has ten, twelve, or fourteen valence electrons, respectively. These hypervalent iodine species not only vary in the number of valence electrons (N) of the central atom (X), in this case (I), as stated,

but also the number of ligands (L) and their chemical properties. According to the Martin Arduengo N-X-L designation, four general structures for hypervalent iodine species (**101-104**), shown below, are considered to be the most important for organic chemistry.[1] The first two species, 8-I-2 (**101**) and 10-I-3 (**102**) are known as iodinanes, which are considered trivalent iodine derivatives and will be the focus of this review. The last two species, 10-I-4 (**103**) and 12-I-5 (**104**) are known as periodinanes are representative of the most common structural types for pentavalent iodine derivatives.[1]

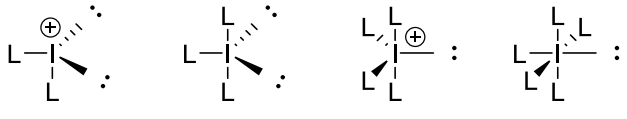


Figure 1: Some structures of hypervalent iodine species with Martin-Arduengo classification.[2]

In the hypervalent bonding model, shown in **Figure 2**, which is the best explanation for iodine (III) species, discussed by Musher in 1969[3] and more recently by Martin[4], only non-hybridized 5p orbitals of the iodine atom participate in bonding. The iodine atom is bound to the least electronegative carbon ligand by a normal covalent bond to the singly occupied equatorial 5p orbital, while each of the other two ligands is bound, one per lobe, to the axial doubly occupied 5p orbital of the iodine atom. This results in a linear three-carbon, four-electron (3c-4e) bond that is considered to be a "hypervalent" bond. These bonds are weaker and longer than normal covalent bonds. This is a result of the lone pair

of electrons in the bonding and non-bonding molecular orbitals that are delocalized to the ligands. Due to this delocalization, a charge distribution is created in which the iodine atom has an approximate charge of +1 while each ligand has an approximate charge of -1/2. For these reasons, trivalent iodine species tend to have a distorted T-shaped geometry. The longer and weaker covalent bonds, that are considered to be hypervalent bonds, provide important reactive character to trivalent iodine species.

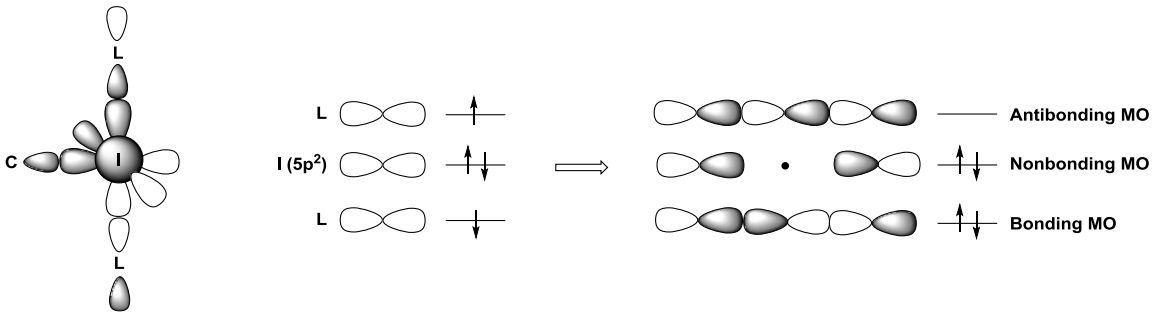


Figure 2: Hypervalent bonding model of hypervalent iodine.

Due to the features of iodine, and hypervalent iodine, already mentioned hypervalent iodine compounds have seen a resurgence in recent years. This is because their high reactivity, benign environmental character, and commercial availability makes them appealing and affordable alternatives to expensive and toxic transition metals. Hypervalent iodine compounds have application for a variety of reactions, such as C-C bond formation, oxidations, iodinations, ligand transfer reactions, and many others.[2]

(Dichloroiodo)benzene (**105** in **Figure 3**) was the first hypervalent iodine compound to be synthesized in 1886 by Willgerodt.[5] Since then, many other hypervalent iodine compounds have been synthesized, such as (diacetoxyiodo)benzene (DIB, **106** in **Figure 3**), in 1892 by Willgerodt,[6] and hydroxyl(tosyloxy)iodobenzene (Koser's reagent or HTIB, **107** in **Figure 3**), are just two, of many, other λ^3-iodanes. In the IUPAC nomenclature λ^n notation is used for the designation of a heteroatom in a non-standard valence state n. Two examples of popular λ^5-iodanes are 2-iodoxybenzoic acid (IBX, **108** in **Figure 3**), first synthesized in 1893 by Hartmann and Meyer,[7] and Dess-Martin periodinane (DMP, **109** in **Figure 3**), first synthesized in 1983 by Dess and Martin.[8]

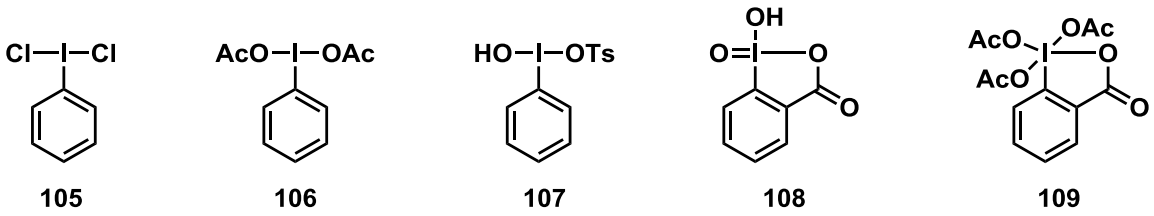
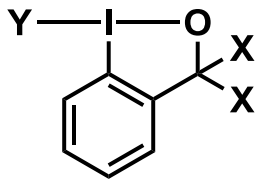


Figure 3: Examples of common λ^3-iodanes and λ^5-iodanes.

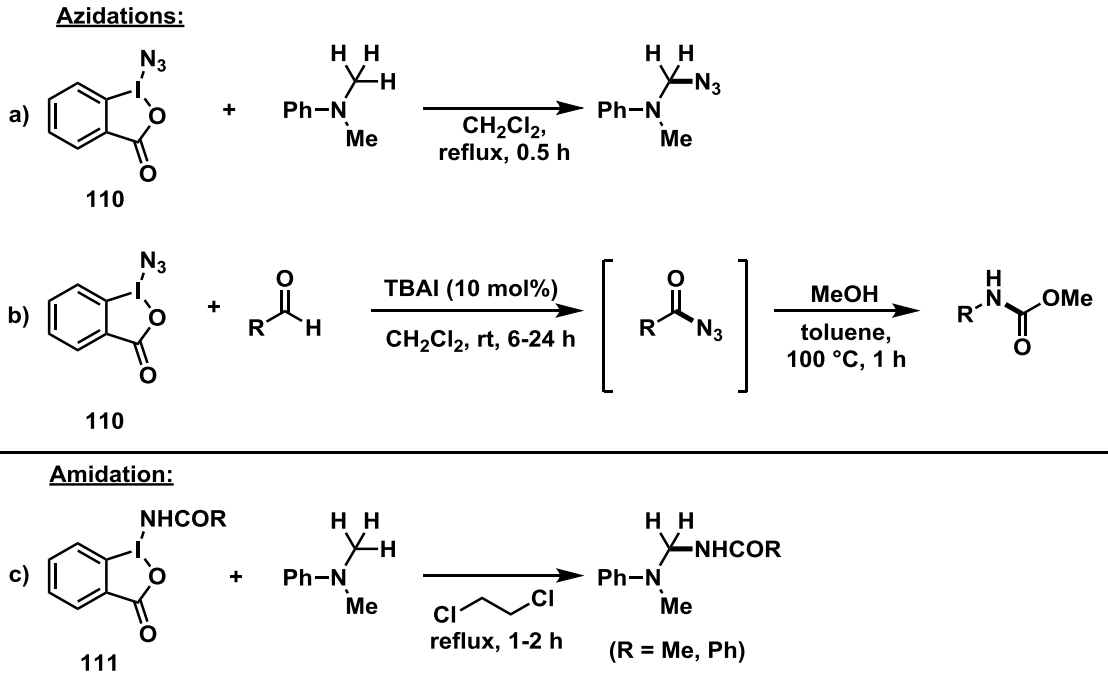
In addition to IBX **108** and DMP **109**, a wide array of heterocyclic organohypervalent iodine compounds have been synthesized and used for organic synthesis. Benziodoxoles (**Scheme 1**) are five-membered hypervalent iodine (III) reagents that have been used as efficient electrophilic atom-transfer reagents in the conversion of a variety of organic substrates.



X = Me, CF_3; 2X = O
Y = OH, OAc, N_3, CN, Cl, NHR, CF_3, etc.

Scheme 1: Examples of benziodoxoles.

Azidations[9,10] and amidations[11] are examples of some of these transformations (**Scheme 2**). In 1996, Zhdankin and co-workers demonstrated that **110** could be reacted with *N*,*N*-dimethyl aniline, under reflux conditions, to obtain the corresponding product of C-H azidation (**Scheme 2a**).[9] In 2015, Zhdankin and co-workers demonstrated that **110** could be reacted with aldehydes to yield acyl azides which could be further reacted to produce carbamates (**Scheme 2b**).[10] In 1997, Zhdankin and co-workers demonstrated that the amidation product of *N*,*N*-dimethyl aniline could be obtained following its reaction with **111** under reflux conditions (**Scheme 2c**).[11] It should be noted that the transformations mentioned are a result of benziodoxoles with exocyclic nitrogen ligands.



Scheme 2: Azidation and amidation reactions using benziodoxoles with exocyclic nitrogen ligands.

As shown in **Figure 4** below, a number of bicyclic benziodoxoles have been reported. The preparation of iodosodilactone, **112**, was first prepared by Agosta in 1965.[12] In 2012, Zhang and co-workers reported a different method for the preparation of **112**, confirmed its structure, and tested its reactivity.[13] Zhang and co-workers demonstrated that **112** could be used as an efficient and recyclable coupling reagent for the preparation of esters, amides, macrocyclic lactones, and peptides.[13] In fact, **112** was used for the solid-state synthesis of peptides without racemization.[13] In 2014, Zhang and co-workers also demonstrated that **113** and **114** could be used for the synthesis of dipeptides.[14]

In 2015, Zhang and co-workers demonstrated **115** to be an improvement upon their previous reagent, **112**, in terms of peptide coupling as it gave higher yields with significantly lower reaction times and at room temperature, as opposed to needing to be heated. It was also reported that, like **112**, **115** can also be regenerated from the reaction mixture.[15] Furthermore, in 2018 Zhang and co-workers showed that **115** could be used for solid-phase peptide synthesis.[16] In 1982, Martin and co-workers reported a method for the synthesis of **116**.[17] Later, in 1986, Martin and co-workers reported a method for the synthesis of **117**, as well as its crystal structure.[18]

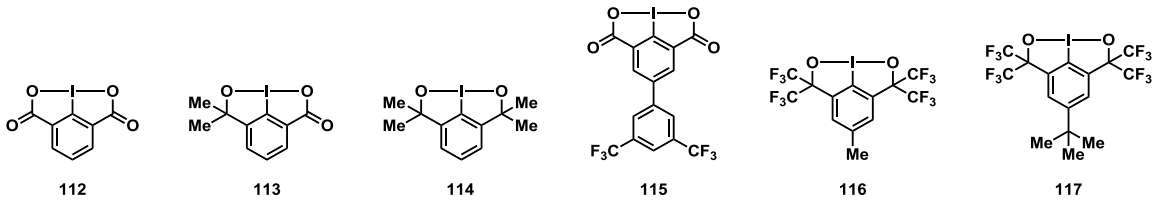


Figure 4: Examples of known bicyclic benziodoxoles.

Five-membered hypervalent iodine(III) heterocycles with heteroatoms other than oxygen are also known. Among these non-oxygen heteroatoms are phosphorous,[19] sulfur,[20] boron,[21,22] and nitrogen.[23-25] A number of nitrogen containing heterocyclic iodine(III) compounds have been reported.

2. Results and Discussion: Bicyclic Benziodazole

2.1 Introduction

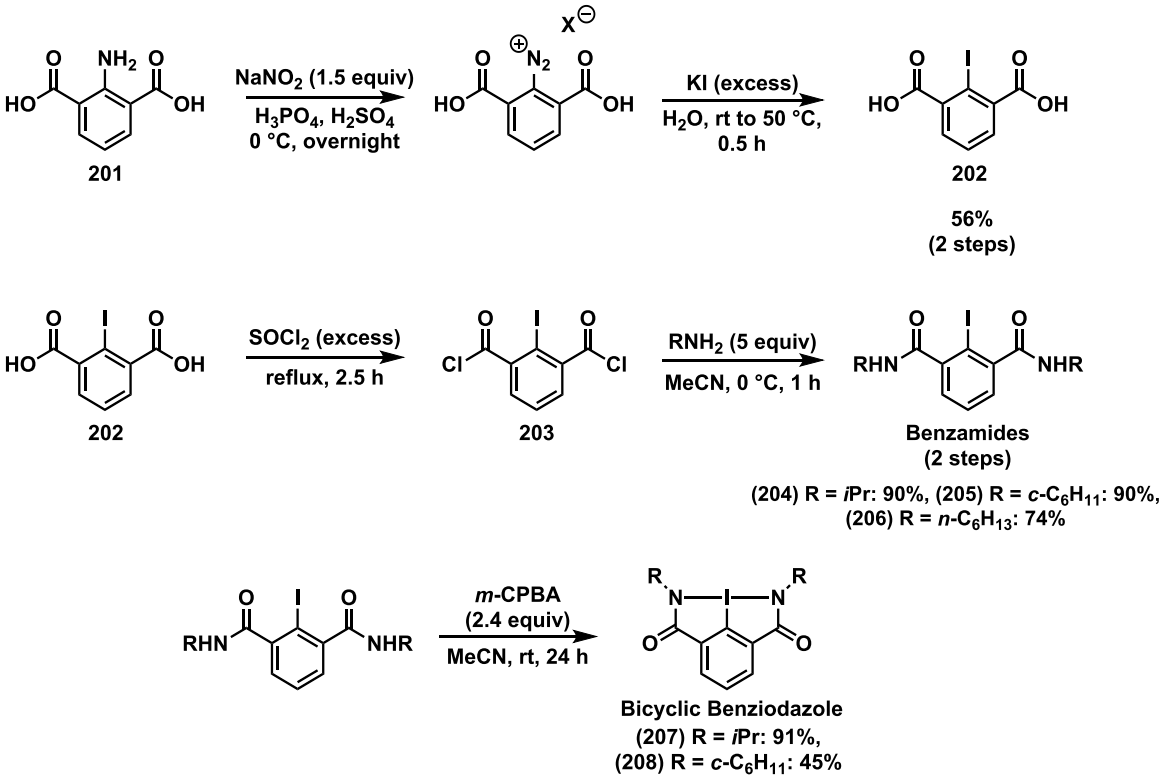
Esters and amides are critically important functional groups, not only in synthetic chemistry but also in everyday life. Parabens are esters that have been used for food preservatives,[26] millions of tons of polyester are produced annually,[27] around one-quarter of pharmacological syntheses involve esters,[28-30] esters are also commonly used in the fragrance industry, and for the synthesis of fatty acids.[31] Amide functional groups are present in biologically significant compounds such as amino acids, and by extension proteins and peptides.[32] Amides can also be used as protecting groups or in the synthesis of polymers.

Due to the importance of esters and amides many procedures have been developed for their synthesis. Fischer, Steglich, Mitsunobu, Yamaguchi, Schotten-Bauchmann reactions are just some of the many methods used to make esters and amides.

2.2 Preparation

The desired bicyclic benziodazole was prepared from commercially available 2-aminoisophthalic acid in five steps as shown in **Scheme 1**. The conversion of 2-aminoisophthalic acid (**201**) to 2-iodoisophthalic acid (**202**) occurs in two steps during which the iodination of the amino group occurred via a diazonium salt intermediate (**Scheme 3**).[33] The carboxylic acid functional groups of the 2-iodoisophthalic acid were first converted to acyl chloride functional groups (**203**) using thionyl chloride (**Scheme 3**).[34] These acyl chloride functional groups were then converted to amides using amines

which yielded the desired benzamide products (**204**-**206**, **Scheme 3**). Lastly, *m*-CPBA was used to oxidize the benzamide to the desired bicyclic benziodazole products (**207**, **208**; **Scheme 3**).[34]



Scheme 3: The synthetic route from 2-aminoisophthalic acid (**201**) to bicyclic benziodazoles (**207** and **208**).

2.3 Structural Study and Stability

The structure of **207** was confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and X-ray crystallography.[34] A single crystal X-ray diffraction of **207** (**Figure 5**) confirmed the presence of two covalent bonds, one between the iodine and each nitrogen atom. These

bonds had the following bond lengths: I(1)-N(1) = 2.184 (4) Å and I(1)-N(2) = 2.177 (4) Å.[34] These bond lengths are similar to those previously reported for benziodazoles.[9,35-37] The bond angle between corresponding to N(1)-I(1)-N(2) was confirmed to be 153.90 (15)^{o}, which is the most bent among the previously reported bicyclic hypervalent iodine compounds.[13,14,17] Based on the X-ray data **207** has a distorted T-shaped geometry but due to an additional intermolecular coordination between the oxygen atom of a neighboring atom and the iodine atom the overall geometry of the iodine center is pseudo-square planar. The length of this intermolecular coordination can be described as follows: I(1)---O'(1) = 3.107 (3) Å.[34]

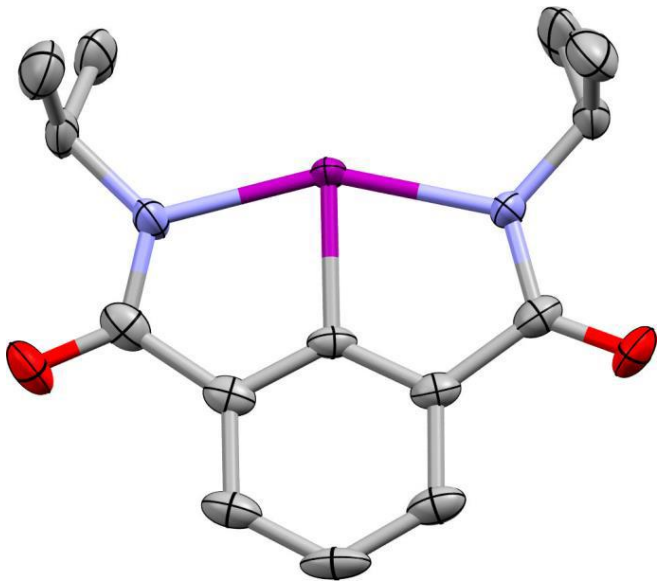


Figure 5: The X-ray crystal structure of *N,N'*-diisopropyl(benzo)bisiodazole (**207**). The ellipsoids are drawn to the 50% probability level. Selected bond lengths and angles: I(1)-(C1) 2.040 (4) Å; I(1)-N(1) 2.184 (4) Å; I(1)-N(2) 2.177 (4) Å; N(1)-I(1)-C(1) 76.89 (18)^{o}; N(2)-I(1)-C(1) 77.02 (18)^{o}; N(1)-I(1)-N(2) 153.90 (15)^{o}.[34]

It was observed, by ^{1}H NMR that **207**, could be stored in $CDCl_3$ or CD_3CN at room temperature for over a month without any signs of decomposition.

2.4 Bicyclic Benziodazole for Esterification and Amidation

2.4.1 Reaction Scope

The reactivity of bicyclic benziodazole **207** was then tested. Similar to the bicyclic benziodoxole **112** prepared by Zhang,[13] **207** was used for oxidatively assisted coupling of carboxylic acids and alcohols or amines to form the corresponding esters (**Figure 6**) and amides (**Figure 7**), respectively.[34]

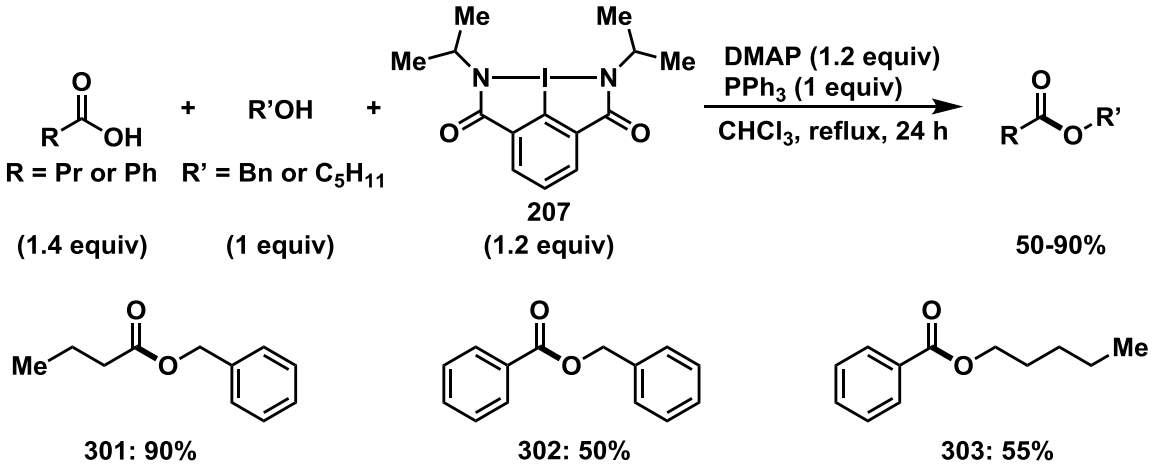


Figure 6: The products of esterification using **207**.

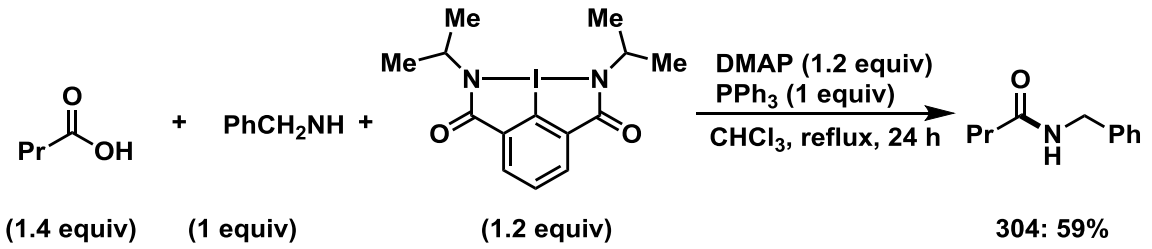


Figure 7: Product of amidation using **207**.

2.4.2 Mechanism

The proposed mechanism for the esterification of alcohols with carboxylic acids is depicted below in **Figure 8**. This mechanism is based on the mechanism proposed by Zhang and co-workers.[13]

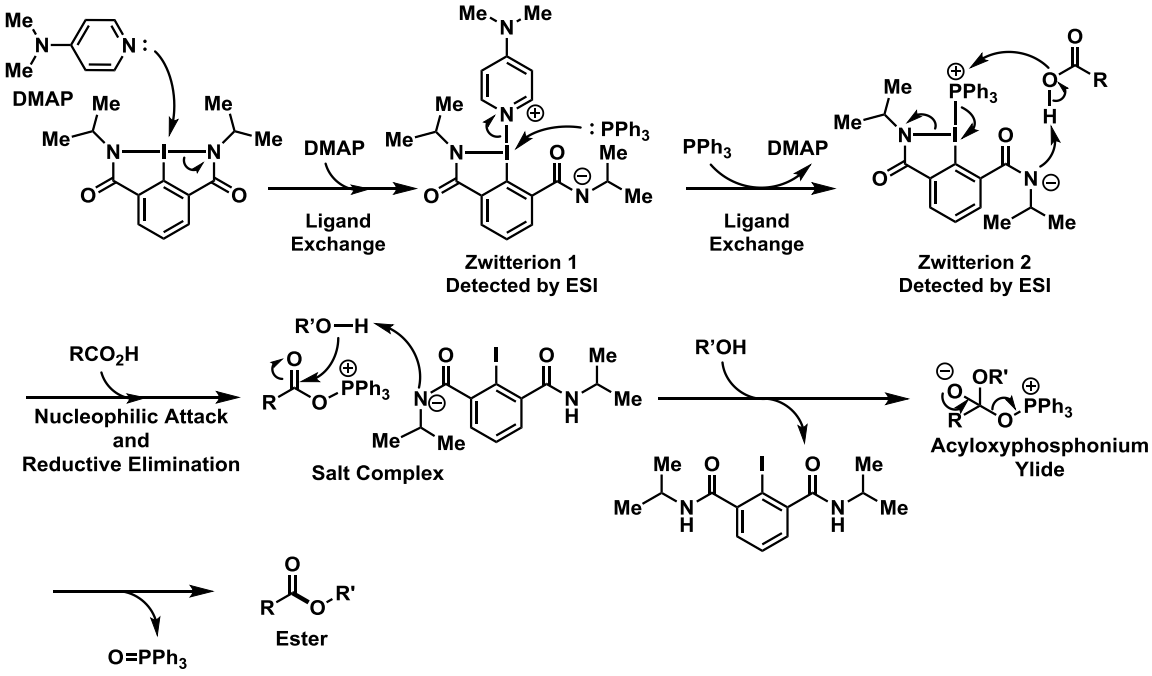


Figure 8: Proposed esterification mechanism using **207**.

Zwitterion 1, detected by HRMS, was formed by DMAP, acting as a nucleophile, having attacked the electrophilic iodine center of **207** which caused a ligand exchange between DMAP and one of the amide moieties. Weiss and Zhdankin have reported similar aryl iodine(III) species with *N*-heteroarenes like pyridine and DMAP.[38,39] The electrophilic iodine center was then attacked by PPh_3 which caused DMAP to leave. The result of this second ligand exchange was Zwitterion 2 which was detected by HRMS and is a more reactive species. Zhang and co-workers reported that from a mixture of **112**, *n*-hexanoic acid, 2-phenylethanol, DMAP, and PPh_3 in $CHCl_3$ under reflux conditions that a peak at *m/z* =570.03 was detected ESI-mass analysis which corresponds to the analogous benziodoxole species $[M + NH_4]^+$.[13] The carboxylic acid would then react with Zwitterion 2 to form the acyloxyphosphonium salt complex after reductive elimination. Then the electrophilic carbonyl carbon of the salt complex was attacked by the alcohol and after the subsequent reductive elimination and release of triphenylphosphine oxide the ester is formed.

Zhang and co-workers conducted a mechanistic study where a L-menthol, a chiral, sterically hindered secondary alcohol, and *n*-hexanoic acid were reacted with **112**, DMAP, and PPh_3 and the corresponding ester was obtained with retained stereochemistry.[13] This supports that the reaction proceeds from the acyloxyphosphonium salt complex intermediate. Zhang and co-workers also conducted a mechanistic study using ^{18}O-labelled 3-phenylpropanol and the previously mentioned conditions. They obtained the corresponding ^{18}O-labelled ester and only normal triphenylphosphine oxide, further supporting the proposed mechanism.[13]

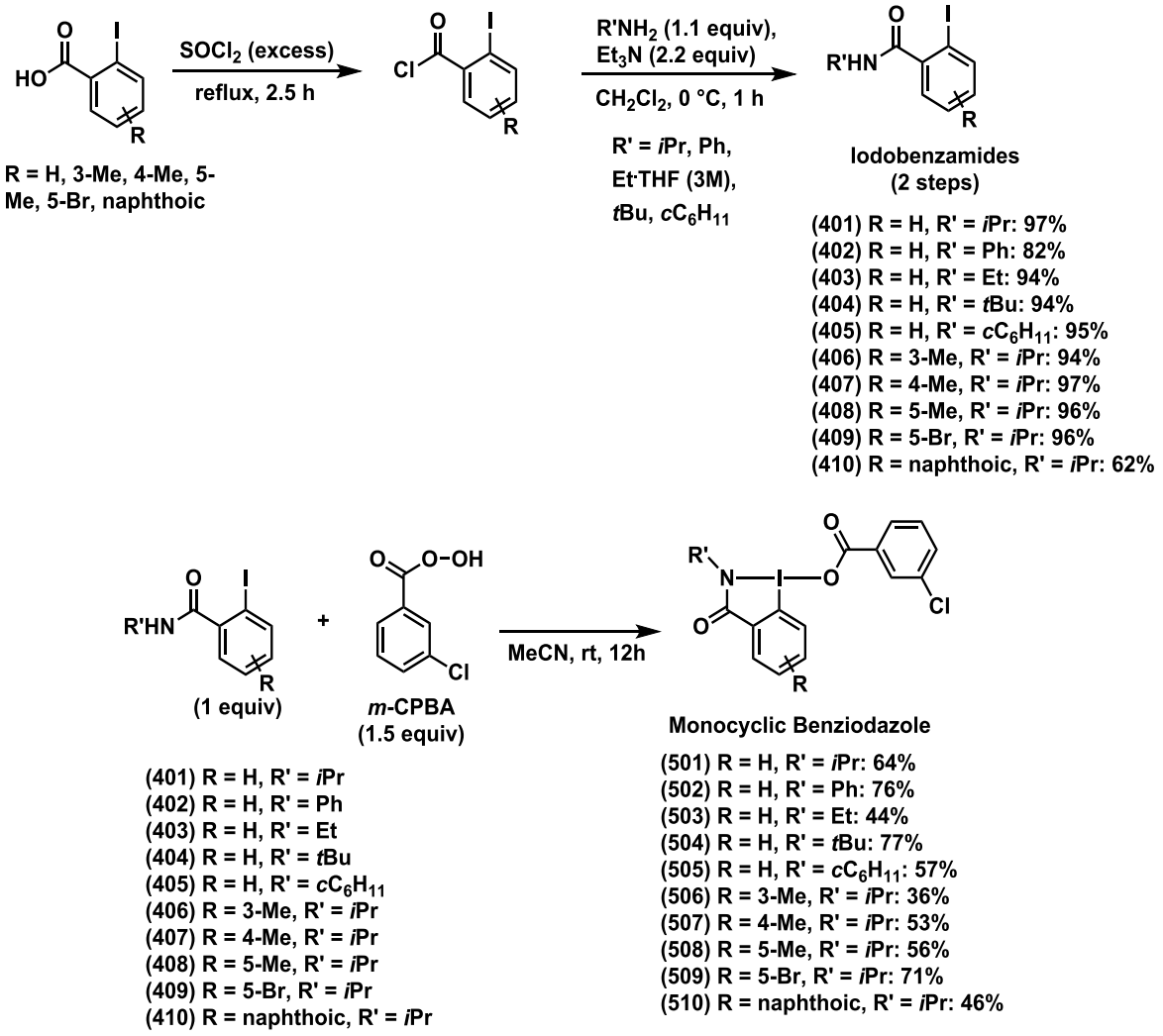
3. Results and Discussion: Monocyclic Benziodazole

3.1 Introduction

As previously stated, esters and amides are important. After synthesizing the first bicyclic benziodazole it was desired to synthesize the corresponding monocyclic analogue by the same oxidative process. Once this was done esterifications and an amidation were conducted to compare the reactivities. After the esterifications and the amidation were conducted, using **501**, the library of monocyclic benziodazoles was expanded.

3.2 Preparation

The desired monocyclic benziodazoles were prepared from commercially available 2-iodobenzoic acids in three steps as shown below in **Scheme 4**. The conversion of the 2-iodobenzoic acid derivatives to the corresponding acyl chlorides occurred as a result of refluxing with thionyl chloride. The acyl chlorides were then converted to the corresponding amides using the appropriate amines in combination with triethylamine. These benzamides were then oxidized with *m*-CPBA which yielded the desired monocyclic benziodazole products.



Scheme 4: The synthesis of various monocyclic benziodazoles from substituted 2-iodobenzoic acid derivatives.

3.3 Monocyclic Benziodazole for Esterification and Amidation

3.3.1 Optimization Study

The ability of **501** to function as a coupling reagent for the condensation of alcohols with a carboxylic acid moiety present was optimized using 1-pentanol (**Table 2**). First, the

importance of a carboxylic acid additive was tested (**Entries 1** and **2**). To prevent competition between the carboxylic acid additive and the carboxylic acid moiety present in **501** *m*-chlorobenzoic acid was used for the carboxylic acid additive. It was found that when a carboxylic acid additive was used the NMR yield was lower (68%, **Entry 1**) than when a carboxylic acid additive was not used (71%, **Entry 2**).

Next, the number of equivalents of **501**, base (DMAP), and phosphine (PPh_3) that would provide the highest yield was tested (**Entries 2-4**, **Table 2**). In **Entry 2**, 2.4 equivalents of **501**, DMAP, and PPh_3 were used and an NMR yield of 71% was obtained. When the number of equivalents of the three components mentioned was decreased to 1.8 (**Entry 3**) to NMR yield remained 71%. The number of equivalents of the three components was further decreased to 1.2 equivalents the NMR yield increased to 84% (**Entry 3**). It should be noted that the reaction mixture becomes a gel-like consistency upon mixing all of the components and stirring. With that in mind, the proposed reason that the yield increased as the number of equivalents of the three components were decreased is that a more favorable ratio of the three components were made soluble and participated in the reaction. This is supported by the fact that the three components are not equally soluble in 1-pentanol.

Based on the previously proposed esterification mechanism using bicyclic benziodazole[34] we wanted to investigate whether a catalytic amount of DMAP could be used. In **Entry 5**, 0.6 equivalents of DMAP was used while **501** and PPh_3 remained at 1.2 equivalents. Under these conditions and NMR yield of 62% was obtained. From this it was concluded that a catalytic amount of base could not be used. Furthermore, if a catalytic

amount of base cannot be used then it is likely that the base does more than activate the initial iodine(III) species.

The base that was used was then alternated in **Entries 6-10** and compared to **Entry 4**. This was done in order to gain a better understanding of the role that the base might play as well as what characteristics of the base are important for the reaction. To this end, **Table 3**, focuses on the base-varied entries of **Table 2**, with the exception of **Entry 10** of **Table 2**, and provides further details about those bases. In all three solvents (H_2O, DMSO, and MeCN), piperidine is the most basic, Et_3N is the second most basic, and pyridine is the least basic. Meanwhile, DMAP and DABCO vary in regards to which is more basic than the other, depending on the solvent. However, in the case of both H_2O and MeCN the difference in the basicity values of DMAP and DABCO is not significantly different (the difference in their pK_{aH} values is less than one). In MeCN, DABCO is the most nucleophilic, piperidine is second, DMAP is third, Et_3N is fourth, and pyridine is the least nucleophilic. With these trends established, the reasoning behind the proceedings from **Entry 4** to subsequent **Entries 6-10** can be explained.

Based on the mechanism proposed by Zhang for their benziodoxole reactions[13] and our group for the bicyclic benziodazole,[34] we proceeded from DMAP (**Entry 4**, **Tables 2** and **3**) to DABCO (**Entry 6**, **Tables 2** and **3**) as DABCO is a significantly stronger nucleophile than DMAP but does not have a significantly different basicity from DMAP. We thought that by using a stronger nucleophile that the first ligand exchange would occur more favorably and reduce the possibility for equilibrium. However, the yield was reduced from 84% (**Entry 4**, **Tables 2** and **3**) to 49% (**Entry 6**, **Tables 2** and **3**), which brought the

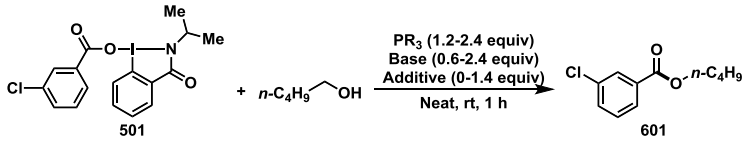
importance of the nucleophilicity of the base into question. To test if basicity was the most important characteristic Et_3N was used next (**Entry 7**, **Tables 2** and **3**) as it is more basic than DMAP (and DABCO) but does not have a significantly different nucleophilicity in comparison to DMAP. The yield improved to 59% (**Entry 7**, **Tables 2** and **3**) compared to the reaction with DABCO, but was still worse than when DMAP was used, which brought the importance of the basicity of the base into question. In order to gain more evidence regarding the lack of importance of base nucleophilicity and basicity, piperidine was used next (**Entry 8**, **Tables 2** and **3**), as it is more basic and nucleophilic than DMAP. In accordance with the previously observed results a yield of 57% was obtained. With this evidence in mind, pyridine, which is less basic and less nucleophilic than DMAP, was used (**Entry 9**, **Tables 1** and **3**), and a yield of 91% was obtained, an improvement upon the DMAP conditions. This result gave rise to considerations for factors other than just basicity and nucleophilicity of the bases that were tested, such as, how soluble the base became in the reaction mixture (and overall reaction mixture solubility), aromaticity, and state of matter. One possible reason for why DABCO had such a low yield is because it appeared as though not all of the solid became a gel-like substance in the reaction mixture, as is usually the case with the other bases. This is supported by the trend that, with the exception of DMAP, liquid bases provided higher yields than DABCO. Due to DMAP not following this trend it is believed that aromaticity, a characteristic shared between DMAP and pyridine, is a critically important feature of the base used, likely due to the planarity intrinsic to aromatic compounds which would allow for the nucleophile to approach the electrophilic iodine center and induce ligand exchange. It is believed that the reason that

pyridine provides a higher yield is because of the higher degree of solubility of the reaction mixture when it is used as opposed to DMAP. This is supported by the solubility of **501** in pyridine. After a variety of organic amine bases were tested, *t*BuOK, an inorganic base, was tested (**Entry 10**, **Table 2**). A yield of 9% was obtained which is not surprising as the *t*BuOK did not become solubilized by the reaction mixture. Next, an alternative phosphine was tested.

Again, with the previously proposed mechanisms in mind, an alternative phosphine was investigated to see if the yield could be improved. It was believed that a more nucleophilic and less sterically bulky phosphine would improve the yield by making, what would be the second ligand exchange if the proposed mechanism is correct, more favorable. One such phosphine is PBu_3. The conformational energy associated with a *n*-butyl group (~1.75 kcal/mol) is less than that for a phenyl group (3.0 kcal/mol).[48] Additionally, the Tolman cone angle of PBu_3, 132°, is smaller than that of PPh_3, 145°.[49] For these reasons, in addition to being more nucleophilic than PPh_3,[41,45] PBu_3 was used (**Entry 11**, **Table 2**). However, a lower yield of 36% was obtained when PBu_3 was used instead of PPh_3. It is believed that this disparity in yield can be attributed to the moisture sensitivity of PBu_3.

Finally, the need for two nucleophiles to facilitate two ligand exchanges was investigated. In **Entry 12** (**Table 2**), the reaction was run without phosphine. The desired ester was not detected. This is not surprising as an activated carboxylic acid cannot be formed without PPh_3. Then, in **Entry 13** (**Table 2**), the reaction was run without a base which resulted in a 29% yield. This suggests that a base is not necessary but dramatically improves the yield of the reaction.

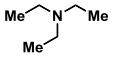
Table 2: Optimization study of the esterification of 1-pentanol with **501**.



Entry	ArI(III) (equiv)	PR_3 (equiv)	Base (equiv)	Basicity in MeCN[a,b]	Nucleophilicity in MeCN[c,d]	Additive (equiv)	Yield (%)[e,f]
1	2.4	PPh_3 (2.4)	DMAP (2.4)	18.18[40,41] (8.0)[41]	5.36[42] (4.76)[42]	*m*-CBA (1.4)	(68%)
2	2.4	PPh_3 (2.4)	DMAP (2.4)	18.18[40,41] (8.0)[41]	5.36[42] (4.76)[42]	0	(71%)
3	1.8	PPh_3 (1.8)	DMAP (1.8)	18.18[40,41] (8.0)[41]	5.36[42] (4.76)[42]	0	(71%)
4	1.2	PPh_3 (1.2)	DMAP (1.2)	18.18[40,41] (8.0)[41]	5.36[42] (4.76)[42]	0	82% (84%)
5	1.2	PPh_3 (1.2)	DMAP (0.6)	18.18[40,41] (8.0)[41]	5.36[42] (4.76)[42]	0	(62%)
6	1.2	PPh_3 (1.2)	DABCO (1.2)	DMAP<DABCO<Et_3N[42] (8.0)[41]	8.26[42] (4.76)[42]	0	(49%)
7	1.2	PPh_3 (1.2)	Et_3N (1.2)	18.46[41,43] (8.0)[41]	5.24[42] (4.76)[42]	0	(59%)
8	1.2	PPh_3 (1.2)	Piperidine (1.2)	18.92[43] (8.0)[41]	7.02[42] (4.76)[42]	0	(57%)
9	1.2	PPh_3 (1.2)	Pyridine (1.2)	12.6[40,41] (8.0)[41]	5.36[h] (4.76)[42]	0	85% (91%)
10	1.2	PPh_3 (1.2)	*t*BuOK (1.2)	N/A (8.0)[41]	N/A (4.76)[42]	0	(9%)
11	1.2	PBu_3 (1.2)	Pyridine (1.2)	12.6[40,41] (>8.0)[g]	5.36[h] (5.89)[42]	0	(36%)
12	1.2	none	Pyridine (1.2)	12.6[40,41] (N/A)	5.36[h] (N/A)	0	(0%)
13	1.2	PPh_3 (1.2)	none	N/A (8.0)[41]	N/A (4.76)[42]	0	(29%)

[a] log values for bases. [b] Numbers in parentheses show phosphine basicity. [c] log values for nucleophilicity of bases. [d] Numbers in parentheses show phosphine nucleophilicity. [e] Numbers in parentheses are ^{1}H NMR yields. [f] Isolated yields. [g] This is supported by data obtained in benzene.[44] [h] This is supported by data obtained in CH_2Cl_2.[45]

Table 3: A focused look at the properties of the bases used in the optimization study of the esterification of 1-pentanol with **501**.

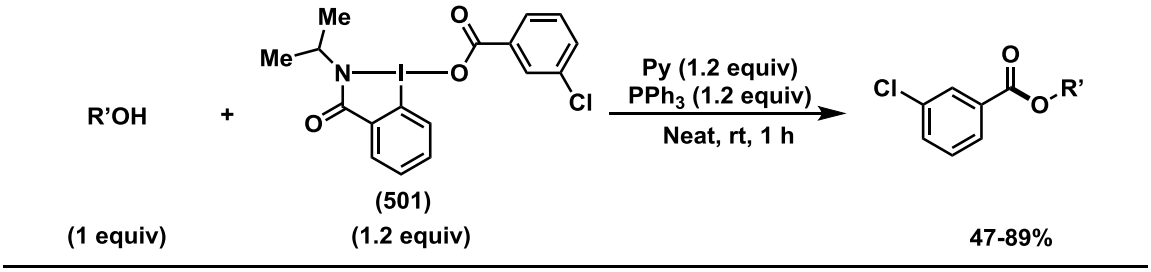
Entry	Base	Structure	Basicity in H_2O[a]	Basicity in DMSO[a]	Basicity in MeCN[a]	Nucleophilicity in MeCN[b]	Yield (%)[ec,d]
4	DMAP		9.6[41]	7.91[40]	18.18[40,41]	5.36	82% (84%)
6	DABCO		8.82[46,47]	8.93[46]	DMAP<DABCO<Et_3N[42]	8.26	(49%)
7	Et_3N		10.7[41,43]	9.0[41]	18.46[41,43]	5.24	(59%)
8	Piperidine		11.12[47]	10.85[47]	18.92[43]	7.02	(57%)
9	Pyridine		5.25[40,41]	3.4[41]	12.6[40,41]	<5.36[x]	85% (91%)

[a] log values for bases. [b] log values for nucleophilicity of bases. [c] Numbers in parentheses are ^{1}H NMR yields. [d] Isolated yields.

3.3.2 Reaction Scope

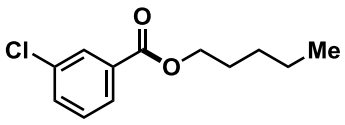
After the reaction conditions were optimized the reaction scope was explored. Five primary alcohols, three secondary alcohols, and one phenol were successfully used for esterification reactions (**Table 4**).

Table 4: Products of esterification using **501**.

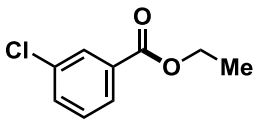


(501)

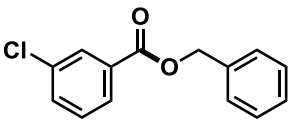
(1 equiv) (1.2 equiv) 47-89%



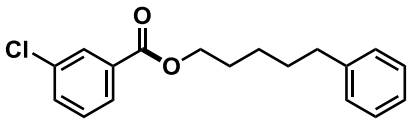
601: 85%



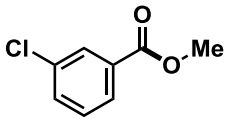
602: 47%



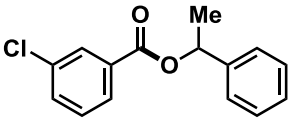
603: 76%



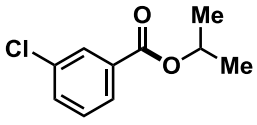
604: 51%



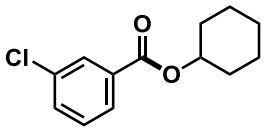
605: 70%



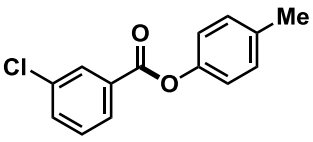
606: 61%



607: 54%

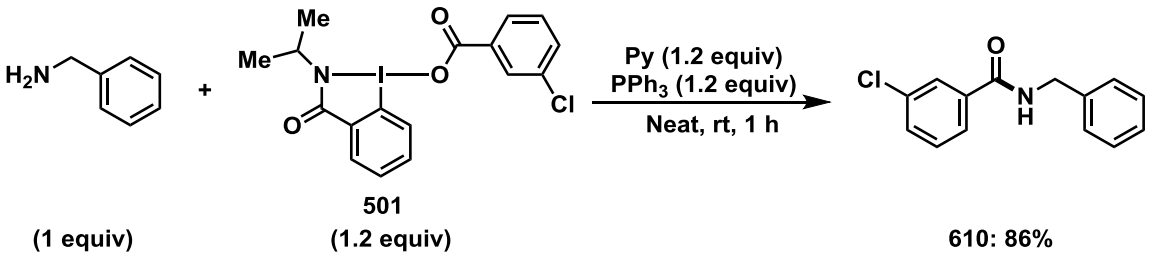


608: 56%



609: 89%

One tertiary alcohol, *t*-butanol, was used for an esterification reaction but none of the corresponding ester was detected by ^{1}H NMR and GCMS. One primary amine was successfully used for an amidation reaction (**Scheme 5**).



Scheme 5: Amidation of benzylamine with **501**, pyridine, and PPh_3 to afford **610**.

The majority of the primary alcohols that were used produced the corresponding esters in higher yields than did the secondary alcohols that were used. It is believed that **502** was produced in a low yield due to the ethanol that was used not having been distilled so the water present inhibited reactivity. It is believed that **506**-**506** were produced in lower yields due to the increased steric hindrance of secondary alcohols when compared to primary alcohols. It is also believed that the reaction with *t*-butanol did not yield the desired ester was due to the steric hindrance of the alcohol. The phenol alcohol, *p*-cresol, gave the corresponding ester, **509**, in high yield, 89%, without detection of dearomatization products. This was an important result; as it supports that the alcohol attacks the electrophilic carbonyl carbon of the aryloxyphosphonium intermediate. Furthermore, the dearomatization of phenols upon reaction with hypervalent iodine species have been reported.[50-52]

The use of the primary amine, benzylamine, produced the corresponding amide in high yield. As expected, given its higher nucleophilicty, benzylamine produced the corresponding amide, **510**, in higher yield, 86% (**Scheme 5)**, than did the analogous esterification using benzyl alcohol, 76% (**Table 4**). With this line of reasoning, it would be expected that the secondary alcohols would have resulted in higher yields of their corresponding esters than the primary alcohols. As this was not the case, it supported the reasoning that the steric hindrance of secondary alcohols was the cause of lower yields. Furthermore, if the argument regarding nucleophilicity were applied to the case of *p*-cresol it would be expected that it would have a lower yield than both primary and secondary alcohols, but this was not the case; the yield was actually the highest among the alcohols, and amine, that were used. Some reasons for this could be that due to its aromatic nature it is intrinsically planar so it is not as sterically hindered as secondary alcohols, π-interactions could be occurring, and that it assists in solubilizing the reaction mixture (a feature that is likely not shared by the other alcohols and amine used).

3.3.3 Mechanism

Two possible mechanisms are proposed below (**Figures 9** and **10**). The first is based on the previously proposed mechanism for the analogous esterification with **112** and those proposed by Zhang.[13]

As shown in **Figure 9**, the electrophilic iodine center iodine center of the trivalent iodine compound is attacked by the nucleophilic pyridine. This results in the carboxylate ligand

being exchanged with the pyridine. The resulting **intermediate Ia** is more reactive than the initial iodine(III) species. This increased reactivity allows for PPh_3 to attack the iodine center which causes the pyridine to be released. This results in an even more reactive species, **intermediate IIa**. **Intermediate IIa** undergoes reductive elimination, going from a trivalent iodine species to a monovalent iodine species. The anionic nitrogen of the monovalent iodine species deprotonates the alcohol which is serving as the nucleophile and attacking the electrophilic carbon of the carboxylate-phosphine intermediate. The resulting intermediate then undergoes another reductive elimination producing triphenyl phosphine oxide and the desired ester. The amidation reaction mechanism is believed to be the same only with an amine being used in the place of an alcohol.

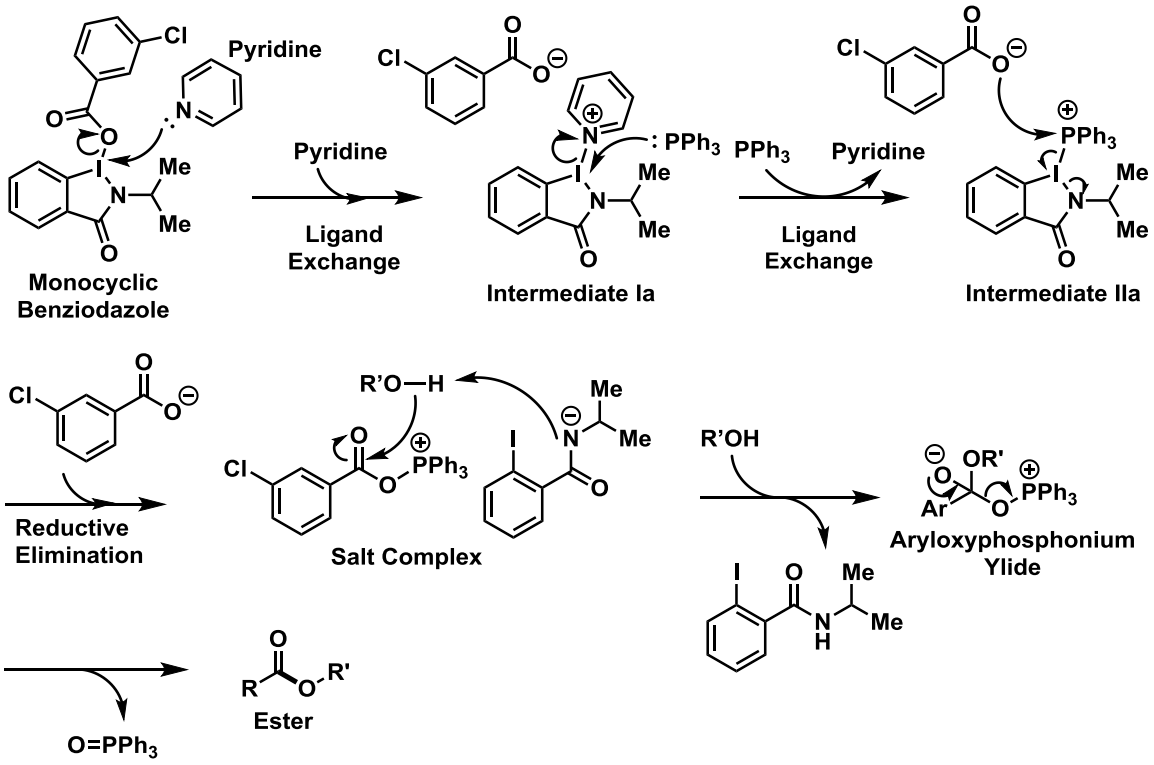
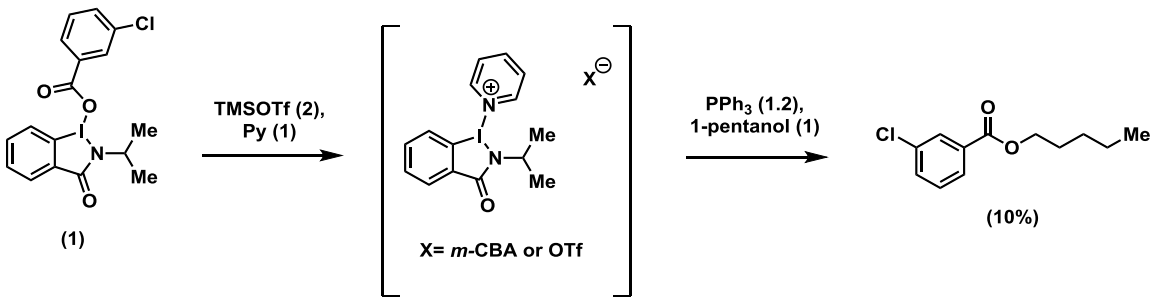


Figure 9: The purposed mechanism for the esterification of alcohols with **501**, pyridine, and PPh_3.

As previously mentioned, Weiss[38] and Zhdankin[39] reported similar compounds to **intermediate Ia** (**Figure 9**). The reaction in **Scheme 6** was ran, using the procedure reported by Zhdankin in 2002,[39] in order to support the first mechanism. The subsequent reactants were added to allow for the esterification of 1-pentanol to occur (**Scheme 6**).



Scheme 6: Synthesis of pentyl 3-chlorobenzoate (**601**) by in situ generation of proposed **intermediate Ia**.

The issue with the first mechanism (**Figure 9**) is that pyridine is less nucleophilic than PPh_3. It is because of this that the second mechanism (**Figure 10**) is proposed.

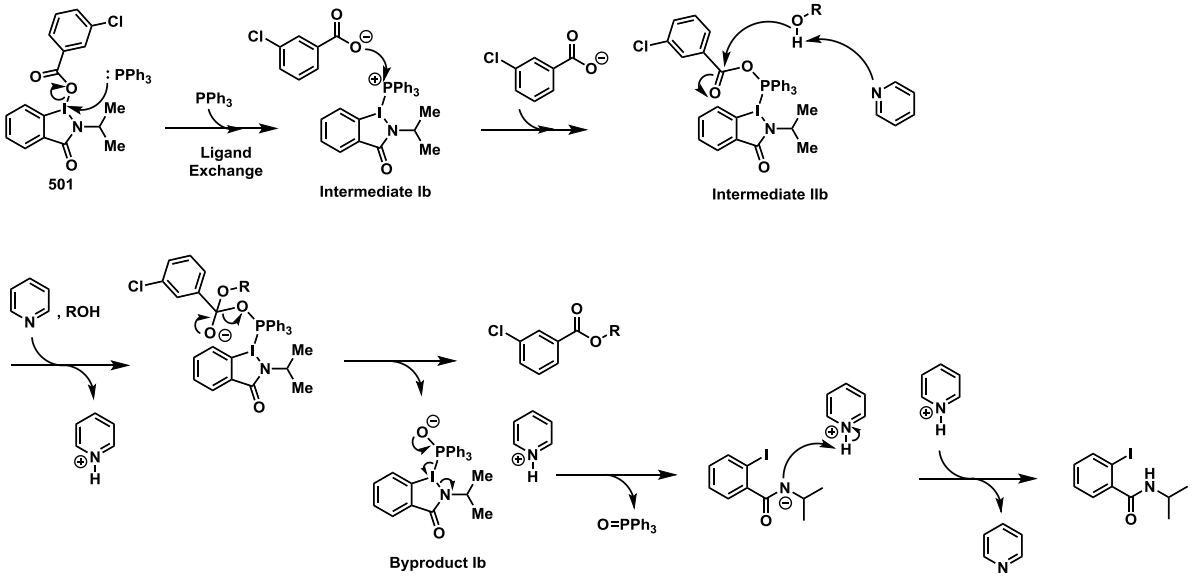
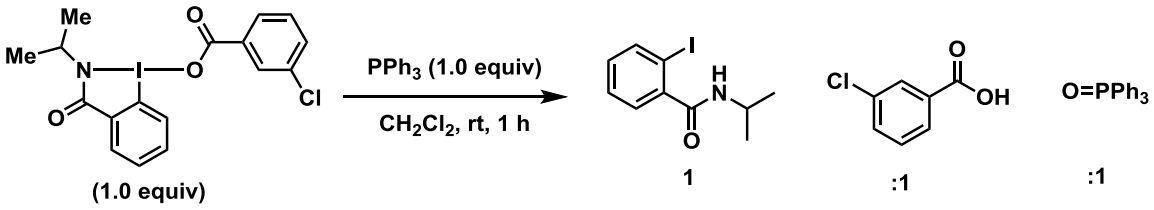


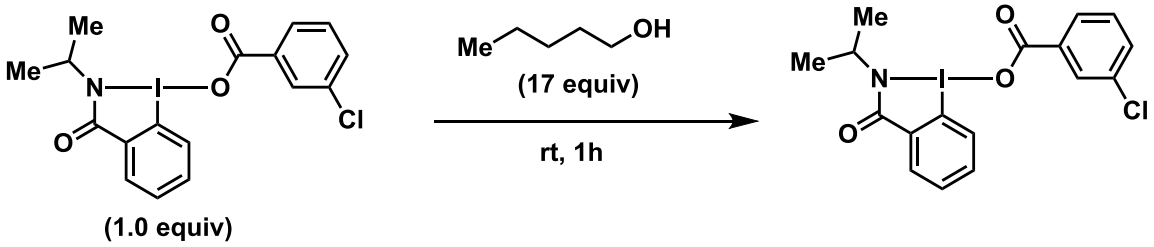
Figure 10: The purposed mechanism for the esterification of alcohols with **501**, pyridine, and PPh_3.

The second mechanism is also supported by HRMS data that was obtained from a mixture of **501** and PPh_3. The mixture produced a fragment of [M]=566, which corresponds to **byproduct Ib**. An attempt to isolate **intermediate IIb** was carried out according to **Scheme 7**, and as shown, the attempt was unsuccessful. **Intermediate IIa/Ib** was also detected in an APCI study with a fragment of $[M + H_2O]^+ = 568$.



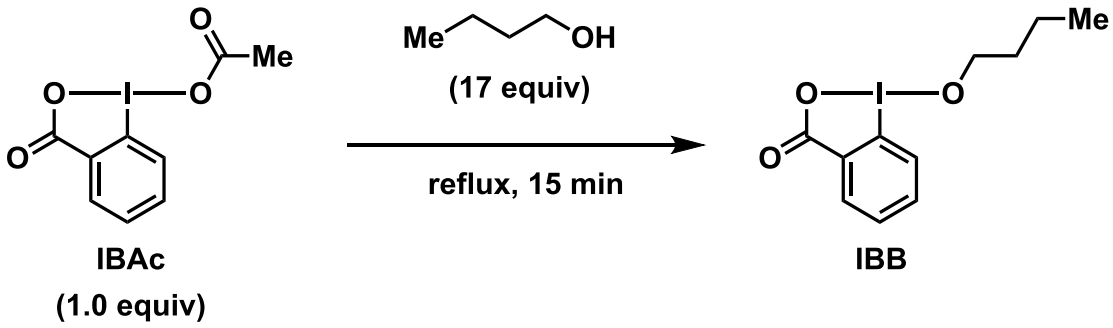
Scheme 7: An attempt to isolate **intermediate IIb**.

Whether or not ligand exchange between the carboxylate of **501** and an alcohol, specifically 1-pentanol, was investigated, as shown in **Scheme 8**.



Scheme 8: Attempted ligand exchange of **501** with 1-pentanol.

In 2017, a similar reaction was reported by Ito and co-workers, who refluxed **IBAc** with *n*-butanol for 15 minutes to produce **IBB**, as shown in **Scheme 9**.[53]



Scheme 9: The previously reported ligand exchange of IBAc with *n*-butanol.[53]

Noticeably, the reaction conditions shown in **Scheme 8** differs from those by Ito and co-workers as it was not conducted under reflux conditions and it was carried out for 1h, to mimic the normal reaction conditions. It is believed that it is due to the lack of reflux conditions that the ligand exchange between **501** and 1-pentanol did not occur as there was not enough energy in the system. As it did not occur with an alcohol that is more nucleophilic than the *m*-CBA anion, it is even less likely that it would occur with *p*-cresol. This differs from what is typically reported to occur between an iodine(III) species and a phenol and is the reason that dearomatizion does not occur. Both of these things support that the alcohol attacks the electrophilic carbonyl carbon rather than the electrophilic iodine center, as previously mentioned. Furthermore, esterification reactions proceeding by an activated carboxylic acid have been reported.[13,15,16,30] It is for these reasons that both mechanisms (**Figures 9** and **10**) depict PPh_3 being attacked by the carboxylate rather than the alcohol.

4. Conclusions and Recommendations

The first reported bicyclic benziodazoles, **207** and **208**, were prepared by the methods described.[34] It was found that **207** was implemented in the condensation of carboxylic acids and alcohols or amines to produce the corresponding esters and amides, respectively.[34] An advantage of **207** over **112** and **115** is that it has good solubility in common organic solvents. After investigating **207**, its monocyclic analogue was prepared, had its structure confirmed by X-ray crystallography, and its reactivity investigated.

The monocyclic benziodazole analogue of **207**, **501**, was prepared by the methods described. Its reactivity was investigated, and it was found to be effective for esterification and amidation reactions. It was found that these reactions could be carried out under neat conditions at room temperature. It is believed that the reason that **501** is able to do this, while **207**, is not is because **501** is a more kinetic product, while **207** is a more thermodynamic product. The reason that **501** is a more kinetic product, than **207**, is due to the carboxylate ligand of **501** being a better leaving group than the amide function group of **207**. After the reactivity of was tested the library of monocyclic benziodazoles was expanded.

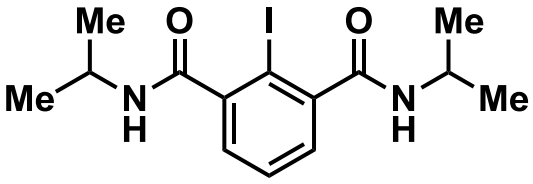
In the future the other monocyclic benziodazoles could have their reactivity investigated. This would allow for comparisons to be made amongst the derivatives and an understanding of the impact of structural differences could be gained. Other possible futures studies could include altering the carboxylate present in **501** to other carboxylates, or even amides.

5. Experimental Details

5.1 Chemicals and Equipment

All reactions were performed with flame-dried glassware. All commercial reagents were ACS reagent grade and were used without further purification. Dichloromethane was distilled from CaH_2 immediately prior to use. Diethyl ether was distilled from Na/benzophenone. Melting points were determined in an open capillary tube with a Mel-temp II melting point apparatus. Infrared spectra were recorded as a KBr pellet on a Perkin-Elmer 1600 series FT-IR spectrometer. NMR spectra were recorded on a Varian Inova 500 or 300 MHz NMR are reported in parts per million (ppm). ^{1}H and ^{13}C NMR chemical shifts are referenced relative to tetramethylsilane.

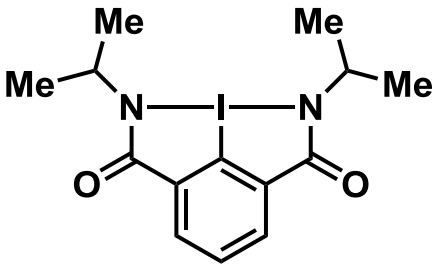
5.2 Procedure for the preparation of 2-iodo-*N*,*N*'-diisopropylisophthalamide (204)



To 2-iodoisophthalic acid (**203**, 580 mg, 0.200 mmol) thionyl chloride (2.0 mL was added). The solution was then refluxed for 2.5 h. Then, the solvent was removed under reduced pressure to give the crude solid acyl chloride. Next, isopropylamine (590 mg, 1.0 mmol) was added at 0 ^{o}C to a stirred mixture of the crude acyl chloride (660 mg, 0.200 mmol) in MeCN (2.0 mL). Following the addition of isopropylamine the reaction mixture continued

to be stirred at 0 ^{o}C for 1 h. The solvent was then removed under reduced pressure to give a solid residue which was recrystallized from a dichloromethane/hexane solution to afford the pure amide **204**. Yield 740 mg (90%, 2 steps), isolated as a white solid, mp 259.5-260.4 ^{o}C; IR (neat) cm^{-1}: 3277, 3067, 2970, 2936, 2876, 1645, 1539; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.1 Hz, 1H), 7.27 (d, *J* = 7.1 Hz, 2H), 5.79 (d, *J* = 7.0 Hz, 2H), 4.34-4.21 (m, 2H), 1.29 (d, *J* = 7.0 Hz, 12H); 13C NMR (75 MHz, CDCl3): δ 168.8, 144.5, 128.5, 128.2, 90.7, 42.3, 22.6; HRMS (APCI-positive): calcd for C14H20IN2O2 ([M+H])+: 375.0569, found: 375.0574.[34]

5.3 Procedure for the Preparation of *N*,*N*'-diisopropylbenziodazole (207)



2-iodo-*N*,*N*'-diisopropylisophthalamide **204**, (670 mg, 0.20 mmol) was added to a solution of *m*-CPBA (830.0 mg, 0.480 mmol) in MeCN (3.0 mL). The reaction mixture was then stirred at room temperature for 24 h. After the reaction was completed, the solvent was removed under reduced pressure to give a solid residue. Then diethyl ether was added to the solid residue to prepare a suspended solution, which was filtered, washed with diethyl ether several times, and dried in vacuum to give product **207**. Yield 680 mg (91%), isolated as a white solid, mp 143.8 °C (decomp.); IR (CH2Cl2) cm-1: 3071, 3039, 2965, 2929, 2872, 1626, 1584; 1H NMR (500 MHz, CDCl3): δ 8.32 (d, *J* = 7.1 Hz, 2H), 7.90 (t, *J* = 7.1

Hz, 1H), 4.41 (sept, *J* = 6.8 Hz, 2H), 1.41 (d, *J* = 6.8 Hz, 12H); 13C NMR (75 MHz, CDCl3): δ 162.8, 132.7, 132.2, 131.2, 113.1, 46.3, 24.5; HRMS (APCI): calcd for C14H18IN2O2 ([M+H])+: 373.0413, found: 373.0398.[34]

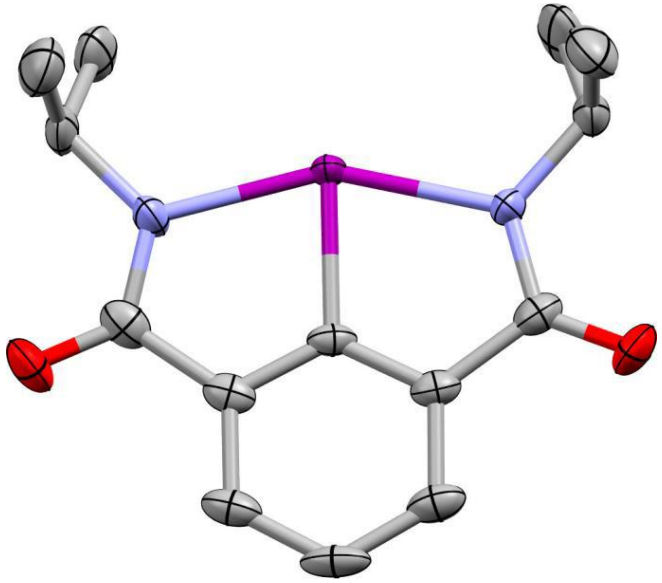


Figure 11: The X-ray crystal structure of *N,N'*-diisopropyl(benzo)bisiodazole (**207**). The ellipsoids are drawn to the 50% probability level.[34]

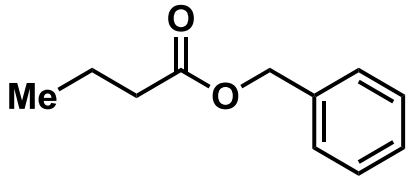
Single crystals of product **207** suitable for X-ray crystallographic analysis were obtained by slow crystallization from dichloromethane solution. X-ray diffraction data for **207** were collected on Rigaku RAPID II Image Plate system using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 173 K. The structure was solved by DIRDIF v2008.3[1] and refined using SHELXL-2014/7[2]. Crystal data for **207** C14H17IN2O2, orthorhombic, space group Pna21, *a* = 17.695(2) Å, *b* = 9.0710(10) Å, *c* = 9.1760(10) Å, α = 90 °, β = 90 °, γ = 90 °, *V* = 1472.9(3) Å3, *Z* = 4, 12610 reflections measured, 3294 unique reflections,

2580 I > 2/s(I), 176 parameters, 1 restraints; Flack Parameter 0.04(2); GooF = 1.038, final R1 = 0.0223, Rw (all) = 0.0510. CCDC 1821160.[34]

5.4 Typical Procedure for Esterifications and Amidations with Bicyclic Benziodazole

A mixture of **207** (67 mg, 0.180 mmol) and DMAP (22 mg, 0.180 mmol) in $CHCl_3$ (5.0 mL) was stirred at reflux for 1 h. Then, 0.210 mmol of carboxylic acid (butyric acid or benzoic acid), PPh_3 (39 mg, 0.150 mmol), and 0.150 mmol of alcohol (1-pentanol or benzyl alcohol) or 0.150 mmol of amine (benzyl amine) were added to the solution. The reaction mixture was then stirred at reflux for 24 h. After reaction, saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by preparative TLC (hexane/ethyl acetate = 1:1) afforded the analytically pure **301**, **302**, **303**, or **304**.[34]

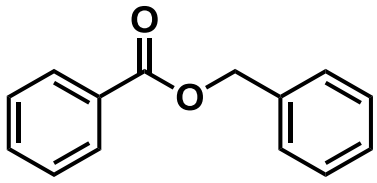
Benzyl butyrate (**301**)[34]



Reaction of butyric acid (19 mg, 0.210 mmol) and benzyl alcohol (16 mg, 0.150 mmol) according to the general procedure afforded 24 mg (90%) of product, isolated as a colorless oil; IR (neat) cm-1: 3067, 3036, 2966, 2935, 2877, 1738, 1258, 1172; ^{1}H NMR (300 MHz,

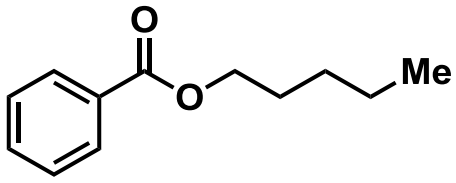
CDCl3): δ 7.40-7.29 (m, 5H), 5.12 (s, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.76-1.60 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 173.5, 136.2, 128.5, 128.2, 66.1, 36.2, 18.5, 13.7.

Benzyl benzoate (**302**)[34]



Reaction of benzoic acid (26 mg, 0.210 mmol) and benzyl alcohol (16 mg, 0.150 mmol) according to the general procedure afforded 16 mg (50%) of product, isolated as a colorless oil; IR (neat) cm-1: 3090, 3062, 3032, 2954, 1720, 1602, 1452, 1272, 1110, 712; ^{1}H NMR (500 MHz, CDCl3): δ 8.08 (d, *J* = 6.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.47-7.31 (m, 7H), 5.37 (s, 2H); ^{13}C NMR (75 MHz, CDCl3): δ 166.4, 136.1, 133.0, 130.2, 129.7, 128.6, 128.4, 128.2, 128.2, 66.7.

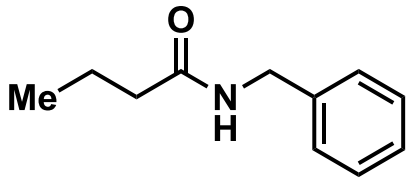
Pentyl Benzoate (**303**)[34]



Reaction of benzoic acid (26 mg, 0.210 mmol) and 1-pentanol (13 mg, 0.150 mmol) according to the general procedure afforded 16 mg (55%) of product, isolated as a colorless oil; IR (neat) cm-1: 3070, 2959, 2933, 2783, 2862, 1722, 1603, 1452, 1274, 1109, 710; ^{1}H

NMR (500 MHz, CDCl3): δ 8.08 (d, *J* = 6.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.47-7.31 (m, 7H), 5.37 (s, 2H); ^{13}C NMR (75 MHz, CDCl3): δ 166.9, 134.0, 130.7, 129.5, 128.6, 65.3, 28.6, 28.4, 22.5, 15.0.

Benzylbutyramide (**304**)[34]



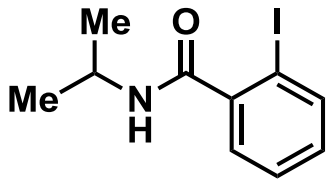
Reaction of benzoic acid (26 mg, 0.210 mmol) and 1-pentanol (**10b,** 13 mg, 0.150 mmol) according to the general procedure afforded 16 mg (55%) of product **11c**, isolated as a colorless oil; IR (neat) cm-1: 3070, 2959, 2933, 2783, 2862, 1722, 1603, 1452, 1274, 1109, 710; 1H NMR (500 MHz, CDCl3): δ 8.08 (d, *J* = 6.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.47-7.31 (m, 7H), 5.37 (s, 2H); ^{13}C NMR (75 MHz, CDCl3): δ 166.9, 134.0, 130.7, 129.5, 128.6, 65.3, 28.6, 28.4, 22.5, 15.0.

5.5 Typical Procedure for the Preparation of 2-Iodobenzamides

To an excess of thionyl chloride, substituted 2-iodobenzoic acid (1 equiv) was added and refluxed for 2.5 h. After the reaction was completed the solvent was removed under reduced pressure to afford the crude acyl chloride. Dichloromethane was added to the crude acyl chloride and cooled to 0 ^{o}C. Once cooled, Et_3N (2.2 equiv) and the appropriate amine (1.1 equiv) were slowly added to the reaction mixture. Once addition of the amines was completed the reaction continued to be stirred for 1 h. After the reaction was completed

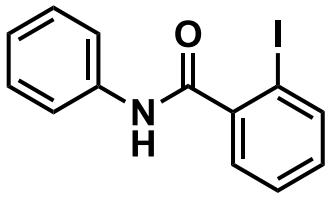
water was added to the reaction mixture. The reaction mixture was extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the pure substituted 2-iodobenzamides.

2-iodo-*N*-isopropylbenzamide (**401**)[54-56]



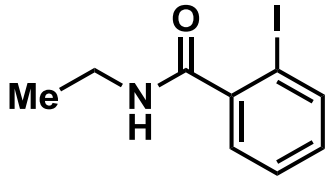
Reaction of 2-iodobenzoic acid (2.976g, 12 mmol) and thionyl chloride according to the general procedure afforded 3.171g (11.9 mmol) of the crude acyl chloride. Reaction of 3.171g of the acyl chloride the corresponding acyl chloride. Reaction of the acyl chloride with isopropylamine (0.774 g, 13.1 mmol) and Et_3N (2.649 g, 26.2) according to the general procedure afforded 3.325g (97%) of product **401**, isolated as a white solid, mp 136.4-137.7 ^oC (Lit. 135-136 ^oC)[54]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 8 Hz, 1H), 7.40-7.34 (m, 2H), 7.08 (t, J = 7.25 Hz, 1H), 5.57 (br. s, 1H), 4.35-4.22 (m, 1H), 4.29 (d, J = 6.5 Hz, 6H); HRMS (APCI-positive): calcd for $C_{10}H_{13}INO$ $([M+H])^+$: 290.0042, found: 290.0063.

2-Iodo-*N*-phenylbenzamide (**402**)[55,57-60]



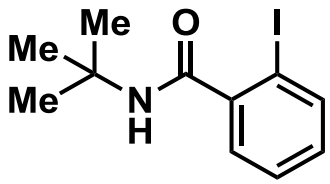
Reaction of 2-iodobenzoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (1.089 g, 4.09 mmol) with aniline (419 mg, 4.50 mmol) and Et_3N (908 mg, 9.0 mmol) according to the general procedure afforded 1.085 g (82%) of product **402**, isolated as a tan solid, mp 144.2-145.0 ^oC (Lit. 144-146 ^oC)[60]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.48-7.34 (m, 4H), 7.22-7.11 (m, 2H).

N-ethyl-2-iodobenzamide (**403**)[55,58,61]



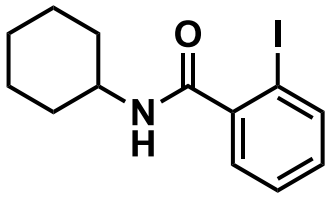
Reaction of 2-iodobenzoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (1.062 g, 3.99 mmol) with $EtNH_2$•THF (2 M) (1.776 g, 4.38 mmol) and Et_3N (0.887 g, 8.77 mmol) according to the general procedure afforded 1.085 g (94%) of product **403**, isolated as a white solid, 114.3-115.5 ^oC (114-116 ^oC)[61]; ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7 Hz, 1H), 7.40-7.32 (m, 2H), 7.12-7.04 (m, 1H), 3.53-3.43 (m, 2H), 1.27 (t, *J* = 7.75 Hz, 3H).

N-(*tert*-butyl)-2-iodobenzamide (**404**)[55,56,59]



Reaction of 2-iodobenzoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (1.063 g, 3.99 mmol) with *t*-butylamine (321 mg, 4.39 mmol) and Et_3N (888 mg, 8.78 mmol) according to the general procedure afforded 1.140 g (94%) of product **404**, isolated as a white solid, mp 122.2-124.1 ºC (Lit. 120-122 ºC)[59]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* =8 Hz, 1H), 7.40-7.32 (m, 2H), 7.06 (t, *J* = 7.75 Hz, 1H), 5.55 (br. s, 1H), 1.48 (s, 9H).

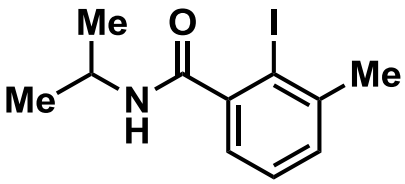
N-cyclohexyl-2-iodobenzamide (**405**)[55,58,59,62]



Reaction of 2-iodobenzoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (1.025 g, 3.85 mmol) with cyclohexylamine (420 mg, 4.23 mmol) and Et_3N (857 mg, 8.46 mmol) according to the general procedure afforded 1.201 g (95%) of product **405**, isolated as a white solid, mp 141.2-142.3 ºC (Lit. 141-143 ºC)[59]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.41-7.33 (m, 2H), 7.08 (t, *J* = 7 Hz, 1H), 7.08 (t, *J* = 7 Hz, 1H), 4.05-3.95 (m, 1H),

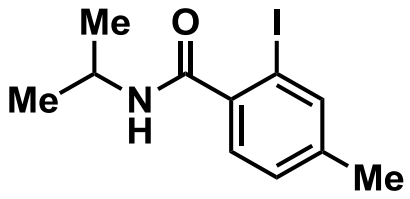
2.13-2.04 (m, 2H), 1.81-1.72 (m, 2H), 1.69-1.60 (m, *1*H), 1.49-1.38 (m, 2H), 1.33-1.15 (m, 3H).

2-iodo-*N*-isopropyl-3-methylbenzamide (**406**)



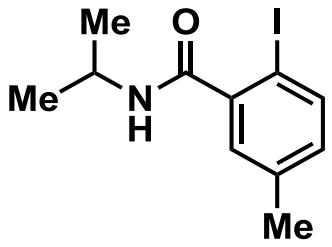
Reaction of 2-iodo-3-methylbenzoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (1.063g, 3.79 mmol) with isoprpylamine (224 mg, 4.17 mmol) and Et_3N (844 mg, 8.34 mmol) according to the general procedure afforded 1.084 g (94%) of product **406**, isolated as a white solid, mp 135.6-137.2 ^oC.; IR (neat) cm^{-1}: 3248, 3069, 2970, 2937, 2875, 1657, 1551, 1459, 1366, 1352, 1331, 1303, 1266, 1204, 1156, 1129, 1012, 919, 858, 805, 780, 738, 718, 685; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28-7.21 (m, 2H), 7.11 (t, *J* = 4.75 Hz, 1H), 5.50 (br. s, 1H), 4.29 (sept., *J* = 5.43 Hz, 1H), 2.48 (s, 3H), 1.28 (d, *J* = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 144.5, 143.1, 130.5, 128.4, 125.2, 99.6, 42.4, 29.4, 22.9; HRMS (ESI-positive): calcd for $C_{11}H_{15}INO$ $([M+H])^+$: 304.0198, found: 304.0190.

2-iodo-*N*-isopropyl-4-methylbenzamide (**407**)[63]



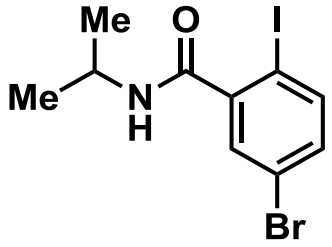
Reaction of 2-iodo-4-methylbenzoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (1.070g, 3.81 mmol) with isopropylamine (248 mg, 4.19 mmol) and Et_3N (849 mg, 8.38 mmol) according to the general procedure afforded 1.118 g (97%) of product **407**, isolated as a tan solid, mp 117.0-119.0 ^oC; IR (neat) cm^{-1}: 3305, 3062, 2973, 2927, 1874, 1637, 1598. 1531, 1484, 1464, 1450, 1389, 1369, 1351, 1329, 1289, 1264, 1178, 1127, 1036, 883, 850, 831, 821, 805, 601, 570; ^1H NMR (500 MHz, $CDCl_3$): δ 763 (s, 1H), 7.20 (d, *J* = 7 Hz, 1H), 7.11 (d, *J* = 8 Hz, 1H), 5.99 (br. s, 1H), 4.19 (octet, *J* = 6.8 Hz, 1H), 2.29 (s, 3H), 1.24 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 141.4, 140.2, 139.6, 92.4, 42.2, 22.6; HRMS (ESI-positive): calcd for $C_{11}H_{15}INO$ $([M+H])^+$: 304.0198, found: 304.0193.

2-iodo-*N*-isopropyl-5-methylbenzamide (**408**)



Reaction of 2-iodo-5-methylbenzoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (2.140 g, 7.63 mmol) with isopropylamine (496 mg, 8.39 mmol) and Et_3N (16.79 mg, 8.39 mmol) according to the general procedure afforded 2.220 g (96%) of product **408,** isolated as a tan solid, mp 147.8-148.7 ºC (Lit. 147-149 ºC); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.5 Hz, 1H), 7.20 (s, 1H), 6.90 (d, *J* = 7 Hz, 1H), 4.28 (octet, *J* = 6.714 Hz, 1H), 2.30 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 6H); HRMS (ESI-positive): calcd for $C_{11}H_{15}INO$ $([M+H])^+$: 304.0198, found: 304.0196.

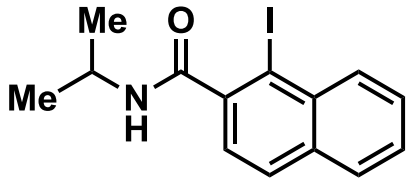
5-bromo-2-iodo-*N*-isopropylbenzamide (**409**)



Reaction of 2-iodo-5-bromobenzoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (1.317 g, 3.81 mmol) with isopropylamine (248 mg, 4.19 mmol) and Et_3N (8.48 mg, 8.38 mmol)

according to the general procedure afforded 1.347 g (96%) of product **409**, isolated as a white solid, mp 187.8-188.5 ^{o}C; IR (neat) cm^{-1}: 3255, 3073, 2971, 1642, 1541, 1453, 1083, 1017, 900, 810, 727; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.5 Hz, 1H), 7.50 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 5.57 (br. s, 1H), 4.27 (octet, *J* = 6.833 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 144.1, 141.1, 134.0, 131.2, 122.6, 90.4, 42.4, 22.6; HRMS (APCI-positive): calcd for $C_{10}H_{12}BrINO$ $([M+H])^{+}$: 367.9147, found: 367.9122.

(**410**)

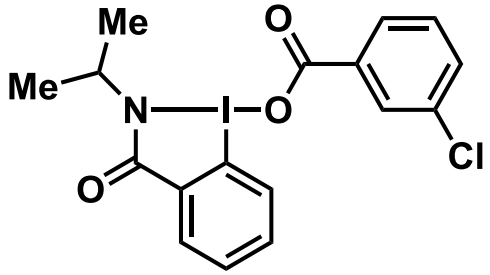


Reaction of 2-iodonaphthoic acid and thionyl chloride according to the general procedure afforded the crude acyl chloride. Reaction of the crude acyl chloride (0.158 g, 0.500 mmol) with isopropylamine (33 mg, 0.550 mmol) and Et_3N (111 mg, 1.10 mmol) according to the general procedure afforded 0.105 g (62%) of product **410**, isolated as a tan solid, mp 191.6-193.3 ^{o}C; IR (neat) cm^{-1}: 3279, 2970, 1642, 1541, 1124, 954, 908, 895, 880, 805, 743; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.86 (s, 1H), 7.84-7.78 (m, 1H), 7.76-7.70 (m, 1H), 7.55-7.50 (m, 2H), 5.68 (br. s, 1H), 4.40-4.30 (m, 1H), 1.33 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 139.3, 139.0, 134.9, 131.9, 128.1, 127.8, 127.4, 127.3, 126.6, 88.8, 42.3, 22.7; HRMS (ESI-positive): calcd for $C_{14}H_{15}INO$ $([M+H])^{+}$: 340.0198, found: 340.0188.

5.6 Typical Procedure for the Preparation of Monocyclic Benziodazoles

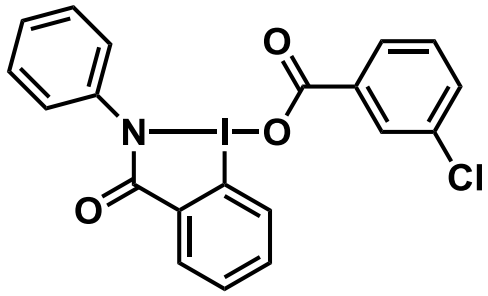
To a solution of substituted 2-iodobenzamide (1.0 equiv) in MeCN, *m*-CPBA (1.5 equiv) was added. The mixture was stirred at room temperature for 12 h. After the reaction was completed the solvent was removed under reduced pressure which resulted in a solid. The solid was filtered several times with diethyl ether to afford the desired product.

(**501**)



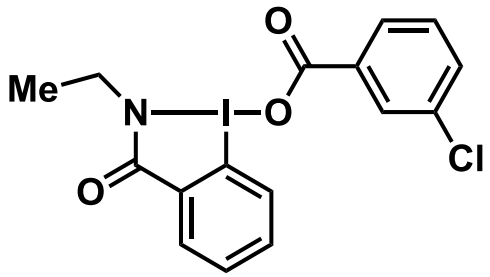
Reaction of **401** (2.637 g, 9.12 mmol) and *m*-CPBA (2.361 g, 13.68 mmol) according to the general procedure afforded 2.590 g (64%) of product **501**, isolated as a white solid, mp 142.0-142.8 ^{o}C; IR (neat) cm^{-1}: 3067, 2967, 2932, 2875, 1627, 1588, 1570, 1296, 1257, 739; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8 Hz, 1H), 8.21 (d, *J* = 6 Hz, 1H), 8.03 (s, 1H), 7.96 (d, *J* = 8 Hz, 1H), 7.75 (t, *J* = 7.75 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.75 Hz, 1H), 4.52 (sept., *J* = 6.625 Hz, 1H), 1.47 (d, *J* = 6.5 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 165.9, 134.4, 133.7, 133.6, 132.3, 131.8, 131.0, 129.9, 129.8, 129.6, 127.9, 116.6, 46.7, 24.3; HRMS (APCI-positive): calcd for $C_{17}H_{16}ClINO_3$ $([M+H])^{+}$: 443.9863, found: 443.9877.

(**502**)



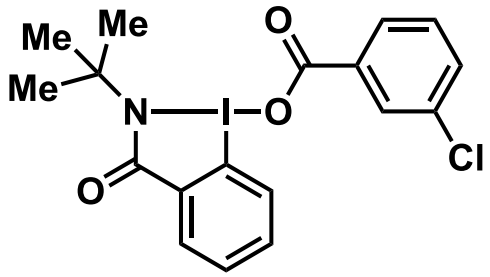
Reaction of **402** (750 mg, 2.32 mmol) and *m*-CPBA (601 mg, 3.48 mmol) in MeCN (17.4 mL) according to the general procedure afforded 841 mg (76%) of product **502**, isolated as a tan solid, mp 161.2-163.0 ^{o}C (decomp. 154.8 ^{o}C); IR (neat) cm^{-1}: 3067, 3033, 1637, 1586, 1569, 1488, 1441, 1507, 1262, 1125, 754, 741, 659; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (d, *J* = 7.5 Hz, 1H), 8.28 (d, *J* = 8 Hz, 1H), 8.03 (s, 1H), 7.99-7.88 (m, 2H), 7.78 (t, *J* = 7.25 Hz, 1H), 7.58-7.37 (m, 6H), 7.32 (t, *J* = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 164.5, 138.1, 135.3, 134.4, 132.9, 132.8, 132.610, 132.572, 131.2, 129.9, 129.8, 129.696, 129.673, 128.0, 127.2, 126.4; HRMS (ESI-positive): calcd for $C_{13}H_{11}INO_2$ ([M-OAr+H])$^{+}$: 339.9834, found: 339.9807.

(**503**)



Reaction of **403** (550 mg, 2.00 mmol) and *m*-CPBA (518 mg, 3.00 mmol) in MeCN (15.0 mL) according to the general procedure afforded .380 mg (44%) of product **503**, isolated as a white solid, mp 76.0-78.0 ºC; IR (neat) cm^{-1}: 3074, 2969, 2935, 2876, 1627, 1590, 1571, 1442, 1319, 1263, 756, 739; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8 Hz, 1H), 8.23 (d, *J* = 8 Hz, 1H), 8.04 (s, 1H), 7.96 (d, *J* = 8 Hz, 1H), 7.86 (t, *J* = 7.75 Hz, 1H), 7.73 (t, *J* = 7.25 Hz, 1H), 7.53 (d, *J* = 6.5 Hz, 1H), 7.41 (t, *J* = 7.75 Hz, 1H), 3.76 (q, *J* = 7.167 Hz, 2H), 1.36 (t, *J* = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 166.3, 134.8, 134.4, 133.5, 132.5, 132.4, 131.9, 131.0, 130.0, 129.8, 129.6, 127.9, 116.8, 38.3, 16.1; HRMS (ESI-positive): calcd for $C_9H_{11}INO_2$ $([M\text{-}OAr+H])^+$: 291.9834, found: 291.9817.

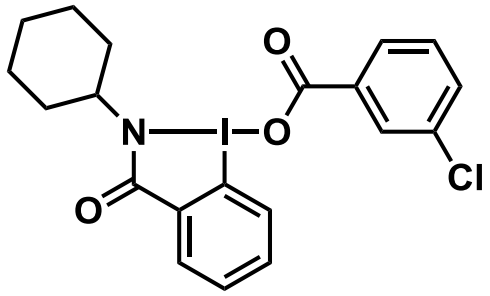
(**504**)



Reaction of **404** (606 mg, 2.00 mmol) and *m*-CPBA (518 mg, 3.00 mmol) in MeCN (15.0 mL) according to the general procedure afforded 705 mg (77%) of product **504**, isolated as

a white solid, mp 170.8-172.0 ^{o}C; IR (neat) cm^{-1}: 3070, 2966, 1628, 1585, 1570, 1438, 1317, 1262, 930, 756, 740; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 7.5 Hz, 1H), 8.04 (s, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.84 (t, J = 7.75 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 7 Hz, 1H), 7.40 (t, *J* = 7.75 Hz, 1H), 1.71 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 165.8, 135.0, 134.5, 134.4, 133.7, 132.3, 131.8, 130.9, 129.6, 129.5, 127.9, 114.8, 58.2, 30.2; HRMS (ESI-positive): calcd for $C_{11}H_{15}INO_2$ ([M-OAr+H])$^{+}$: 320.0147, found: 320.0137.

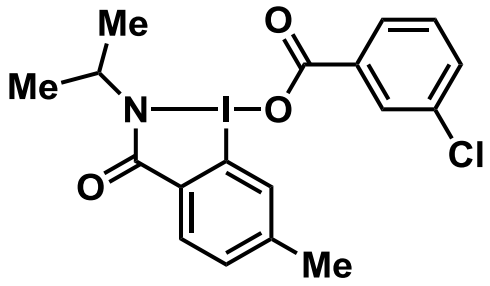
(**505**)



Reaction of **405** (750 mg, 2.28 mmol) and *m*-CPBA (590 mg, 3.42 mmol) in MeCN (17.1) according to the general procedure afforded 633 mg (57%) of product **505**, isolated as a white solid, mp 159.0-160.3 ^{o}C; IR (neat) cm^{-1}: 3071, 2929, 2854, 1629, 1589, 1566, 1439, 1323, 1294, 1621, 1067, 967, 756, 739, 659; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8 Hz, 1H), 8.22 (d, *J* = 7.5 Hz, 1H), 8.04 (s, 1H), 7.96 (d, *J* = 7 Hz, 1H), 7.83 (t, *J* = 7.75 Hz, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 7.75 Hz, 1H), 4.21-4.08 (m, 1H), 2.25-2.15 (m, 2H), 1.95-1.84 (m, 2H), 1.79-1.70 (m, 1H), 1.48 (pent., *J* = 10.875 Hz, 4H), 1.30-1.18(m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 165.9, 134.5, 134.4,

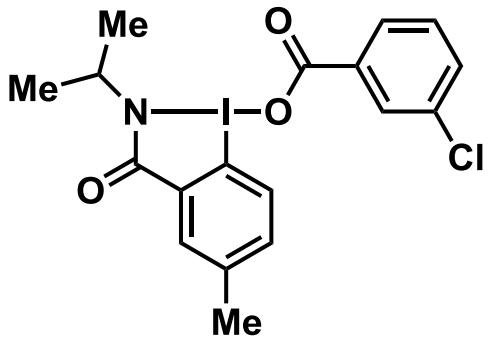
133.7, 133.6, 132.3, 131.8, 131.0, 130.0, 129.8, 129.6, 127.8, 116.9, 54.2, 35.5, 25.7, 25.3; HRMS (ESI-positive): calcd for $C_{13}H_{17}INO_2$ ([M-OAr+H])$^+$: 346.0304, found: 346.0286.

(**507**)



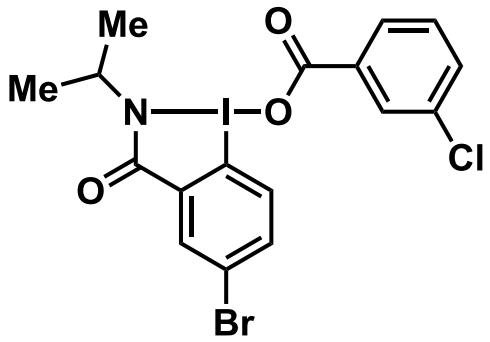
Reaction of **407** (606mg, 2.00 mmol) and *m*-CPBA (518, 3.00 mmol) according to the general procedure afforded 486 mg (53%) of product **507**, isolated as a tan solid, mp 150.2-151.5 ^{o}C; IR (neat) cm^{-1}: 3073, 2964, 2929, 1618, 1569, 1463, 1313, 1295, 1260, 1143, 757, 740, 667; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09-8.01 (m, 3H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.55-7.48 (m, 2H), 7.41 (t, *J* = 7.75 Hz, 1H), 4.50 (sept, *J* = 6.6 Hz, 1H), 2.56 (s, 3H), 1.45 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 166.1, 146.0, 134.4, 133.8, 132.3, 132.1, 131.5, 131.0, 129.9, 129.8, 129.6, 127.8, 116.8, 46.6, 24.4, 22.3; HRMS (ESI-positive): calcd for $C_{11}H_{15}INO_2$ ([M-OAr+H])$^+$: 320.0147, found: 320.0140.

(**508**)



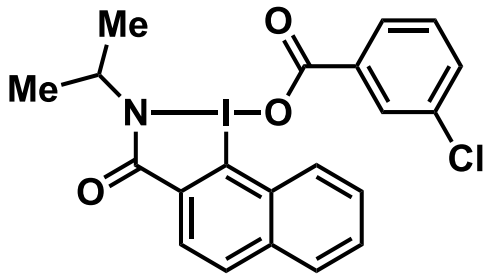
Reaction of **408** (606 mg, 2.00 mmol) and *m*-CPBA (518 mg, 0.150 mmol) in MeCN (15.0 mL) according to the general procedure afforded 513 mg (56%) of product **508**, isolated as a white solid, mp 148.0-15.0 ^{o}C; IR (neat) cm^{-1}: 3067, 2965, 2927, 2874, 1630, 1574, 1456, 1307, 1260, 1143, 756, 740; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8 Hz, 1H), 8.03 (s, 2H), 7.64 (d, *J* = 6.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.75 Hz, 1H), 4.50 (sept, *J* = 6.375 Hz, 1H), 2.54 (s, 3H), 1.45 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 166.1, 141.9, 135.6, 134.3, 133.7, 133.4, 132.3, 132.2, 129.8, 129.605, 129.551, 127.9, 112.8, 46.7, 24.3, 20.9; HRMS (ESI-positive): calcd for $C_{11}H_{15}INO_2$ ([M-OAr+H])$^{+}$: 320.0147, found: 320.0141.

(**509**)



Reaction of **409** (736 mg, 2.00 mmol) and *m*-CPBA (518 mg, 3.00 mmol) in MeCN (15.0 mL) according to the general procedure afforded 738 mg (71%) of product **11a**, isolated as a white solid, mp 151.6-152.6 ^{o}C; IR (neat) cm^{-1}: 3103, 3066, 2968, 2931, 1636, 1617, 1568, 1557, 1464, 1443, 1405, 1305, 1260, 1141, 1070, 959, 903, 813, 755, 742; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 2H), 8.01 (s, 1H), 7.93 (d, *J* = 9 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.75 Hz, 1H), 4.50 (sept, *J* = 6.25 Hz, 1H), 1.46 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 164.5, 137.4, 134.7, 133.3, 132.5, 131.4, 129.8, 129.7, 127.8, 126.4, 114.5, 46.962; HRMS (ESI-positive): calcd for $C_{10}H_{12}BrINO_2$ ([M-OAr+H])$^{+}$: 383.9096, found: 383.9101.

(**510**)



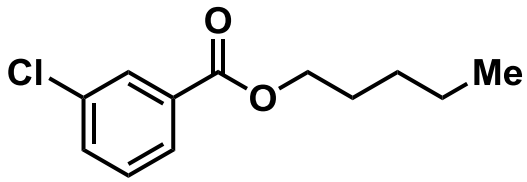
Reaction of **410** (85 mg, 0.250 mmol) and *m*-CPBA (65 mg, 0.375 mmol) in MeCN (1.9 mL) according to the general procedure afforded 56 mg (46%) of product **510**, isolated as a tan solid, mp 153.3-155.0 ^{o}C; IR (neat) cm^{-1}: 3058, 2966, 2922, 1636, 1619, 1569, 1296, 1144, 758, 740; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (s, 2H), 8.15- (d, *J* = 8.5 Hz, 2H), 8.01 (s, 1H), 7.93 (d, *J* = 9 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.75 Hz, 1H), 4.50 (sept, *J* = 6.25 Hz, 1H), 1.46 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 164.5, 137.4, 134.7, 133.3, 132.5, 131.4, 129.8, 129.7, 127.8, 126.4, 114.5, 46.962; HRMS (ESI-positive): calcd for $C_{10}H_{12}BrINO_2$ ([M-OAr+H])$^{+}$: 383.9096, found: 383.9101.

5.7 Typical Procedure for Esterification and Amidation with Monocyclic Benziodazoles

To a test tube containing **501** (80 mg, 0.18 mmol), PPh_3 (47 mg, 0.18 mmol), pyridine (14 mg, 0.18 mmol), and alcohol (0.15 mmol) or amine (0.15 mmol) were added. The mixture was then stirred at room temperature for 1 h. After the reaction was completed, dichloromethane (3.0 mL) was used to transfer the reaction mixture to a separatory funnel. Then saturated $NaHCO_3$ (3.0 mL) was added and the reaction mixture was extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated

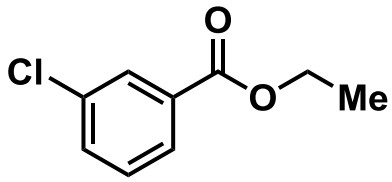
under reduced pressure. Purification by preparative TLC (hexane/ethyl acetate = 3:1) afforded the analytically pure **601-610**.

Pentyl 3-chlorobenzoate (**601**)[64]



Reaction of 1-pentanol (13 mg, 0.150 mmol) according to the general procedure afforded 29 mg (85%) of product **601**, isolated as a colorless oil; IR (neat) cm^{-1}: 2961, 1724, 1576, 1469, 1293, 1256, 1127, 967, 675; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.41-7.35 (m, 1H), 4.32 (t, *J* = 6.5 Hz, 2H), 1.82-1.73 (m, 2H), 1.47-1.34 (m, 4H), 0.94 (t, *J* = 6.75 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 134.5, 132.8, 132.3, 129.643, 129.612, 127.7, 65.6, 28.4, 28.2, 22.4, 14.0; HRMS (APCI-positive): calcd for $C_{12}H_{17}ClO_2$ $([M+H])^+$: 227.0839, found: 227.0846.

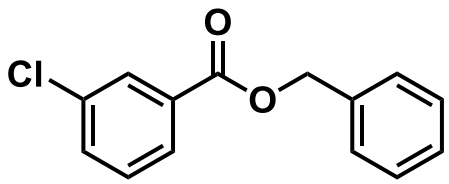
Ethyl 3-chlorobenzoate (**602**)[65]



Reaction of ethanol (7 mg, 0.150 mmol) according to the general procedure afforded 13 mg (47%) of product **11a**, isolated as a colorless oil; IR (neat) cm^{-1}: 2924, 1727, 1573, 1466, 1370, 1293, 1281, 1256, 915, 749; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.53 (d, *J* = 7 Hz, 1H), 7.40-7.36 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.40

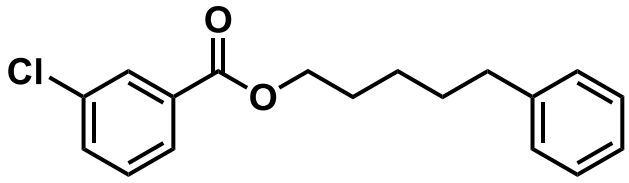
(q, J = 7.2 Hz, 3H); HRMS (APCI-positive): calcd for $C_9H_{10}ClO_2$ $([M+H])^+$: 185.0369, found: 185.0389.

Benzyl 3-chlorobenzoate (**603**)[66]



Reaction of benzyl alcohol (16 mg, 0.150 mmol) according to the general procedure afforded 28 mg (76%) of product **603**, isolated as a colorless oil; IR (neat) cm^{-1}: 2955, 1721, 1576, 1429, 1290, 1278, 1124, 955, 659; ^1H NMR (500 MHz, $CDCl_3$): δ 8.06-8.02 (m, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.42-7.33 (m, 4H), 5.36 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 135.6, 134.5, 133.1, 131.9, 129.734, 129.696, 128.7, 128.4, 128.3, 127.8, 67.1; HRMS (ESI-positive): calcd for $C_{14}H_{11}ClO_2Na$ $([M+Na])^+$: 269.0345, found: 269.0341.

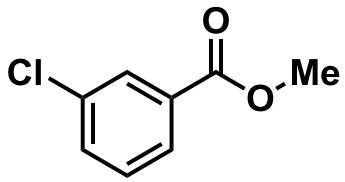
5-Phenylpentyl 3-chlorobenzoate (**604**)



Reaction of 5-phenyl-1-pentyl alcohol (25 mg, 0.150 mmol) according to the general procedure afforded 23 mg (51%) of product **604**, isolated as a colorless oil; IR (neat) cm^{-1}: 2937, 1724, 1576, 1429, 1293, 1256, 1124, 958, 699, 675, 659; ^1H NMR (500 MHz,

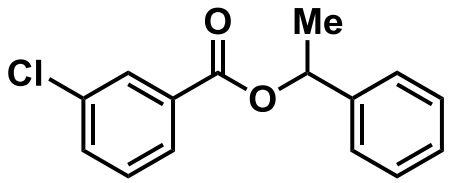
$CDCl_3$): δ 7.99 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.36 (td, *J* = 3 Hz, *J* = 7.75 Hz, 1H), 7.28-7.22 (m, 2H), 7.20-7.12 (m, 3H), 4.31 (td, *J* = 3 Hz, *J* = 6.625 Hz, 2H), 2.68-2.58 (m, 2H), 1.85-1.75 (m, 2H), 1.74-1.64 (m, 2H), 1.53-1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2, 141.1, 133.2, 131.6, 131.0, 128.415, 128.369, 127.141, 127.065, 126.4, 124.5, 64.1, 34.5, 29.8, 27.3, 24.3; HRMS (APCI-positive): calcd for $C_{18}H_{20}ClO_2$ $([M+H])^+$: 303.1152, found: 303.1173.

Methyl 3-chlorobenzoate (**605**)[67,68]



Reaction of methanol (5 mg, 0.150 mmol) according to the general procedure afforded 18 mg (70%) of product **11a**, isolated as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.93 (d, *J* = 7 Hz, 1H), 7.53 (d, *J* = 8 Hz, 1H), 7.41-7.36 (m, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 134.5, 132.9, 131.8, 129.7, 129.7, 127.7, 52.4.

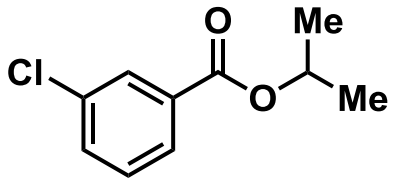
1-Phenylethyl 3-chlorobenzoate (**606**)[69]



Reaction of 1-phenylethyl alcohol (18 mg, 0.150 mmol) according to the general procedure afforded 24 mg (61%) of product **606**, isolated as a colorless oil (Lit. mp 134-136 °C)[69];

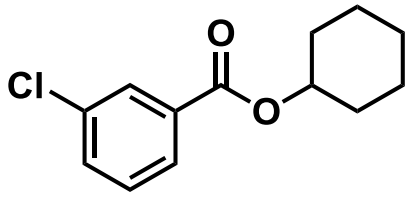
IR (neat) cm^{-1}: 2985, 1723, 1574, 1496, 1456, 1428, 1256, 1129, 697; ^1H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.44 (d, *J* = 8 Hz, 1H), 7.41-7.35 (m, 3H), 7.34-7.29 (m, 1H), 6.13 (q, *J* = 6.5 Hz, 1H), 1.68 (d, *J* = 6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 141.4, 134.5, 133.0, 132.3, 129.7, 129.7, 128.7, 128.1, 127.9, 126.1, 73.5, 22.4; HRMS (ESI-positive): calcd for $C_{15}H_{13}ClO_2Na$ $([M+Na])^+$: 283.0502, found: 283.0489.

Isopropyl 3-chlorobenzoate (**607**)[70]



Reaction of isopropanol (9 mg, 0.150 mmol) according to the general procedure afforded 16 mg (54%) of product **607**, isolated as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 8.02-7.99 (m, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.39-7.34 (m, 1H), 5.25 (sept, *J* = 6.5 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 6H).

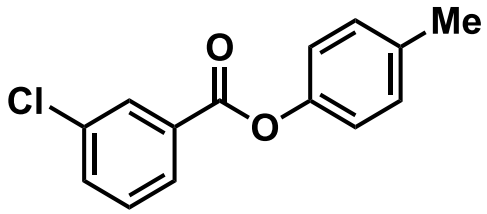
Cyclohexyl 3-chlorobenzoate (**608**)[71]



Reaction of cyclohexanol (15 mg, 0.150 mmol) according to the general procedure afforded 20 mg (56%) of product **608**, isolated as a colorless oil; IR (neat) cm^{-1}: 2937,

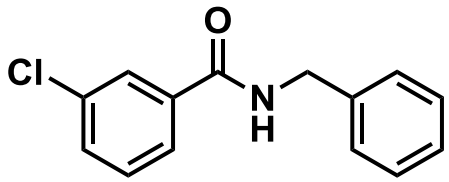
1721, 1576, 1469, 1290, 1253, 1124, 945, 749, 678; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03-8.00 (m, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.40-7.36 (m, 1H), 5.06-4.99 (m, 1H), 1.99-1.91 (m, 2H), 1.84-1.75 (m, 2H), 1.64-1.52, (m, 3H), 1.50-1.40 (m, 2H), 1.39-1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 134.4, 132.747, 132.686, 129.6, 129.6, 127.7, 73.7, 31.6, 25.4, 23.7; HRMS (APCI-positive): calcd for $C_{13}H_{16}ClO_2$ $([M+H])^+$: 239.0839, found: 239.0843.

p-Tolyl 3-chlorobenzoate (**609**)



Reaction of *p*-cresol (16 mg, 0.150 mmol) according to the general procedure afforded 33 mg (89%) of product **609**, isolated as a white solid, mp 75.4-76.0 ^{o}C; IR (neat) cm^{-1}: 2925, 1742, 1578, 1474, 1288, 1251, 1197, 1165, 1106, 811, 743; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18-8.16 (m, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.46-7.41 (m, 1H), 7.22 (d, *J* = 11 Hz, 1H), 7.08 (d, *J* = 8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 149.1, 136.3, 135.3, 134.1, 132.0, 130.7, 130.6 130.4, 128.8, 121.8, 21.4; HRMS (ESI-positive): calcd for $C_{14}H_{12}ClO_2$ $([M+H])^+$: 247.0526, found: 247.0528.

N-Benzyl 3-chlorobenzamide (**610**)[72,73]



Reaction of benzylamine (16 mg, 0.150 mmol) (16 mg, 0.150 mmol) according to the general procedure afforded 32 mg (86%) of product **610**, isolated as a white solid, mp 98.0-99.0 ºC (Lit. mp 98.0-99.0 ºC)[73]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.58 (m, 1H), 7.65 (d, *J* = 6.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.38-7.27 (m, 6H), 6.44 (br. s, 1H), 4.63 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.987, 137.8, 136.1, 134.8, 131.6, 129.9, 128.8, 127.950, 127.8, 127.3, 125.0, 44.3; HRMS (APCI-positive): calcd for $C_{14}H_{13}ClNO$ $([M+H])^+$: 246.0686, found: 246.0706.

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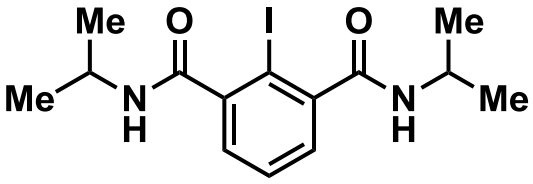
7. Appendices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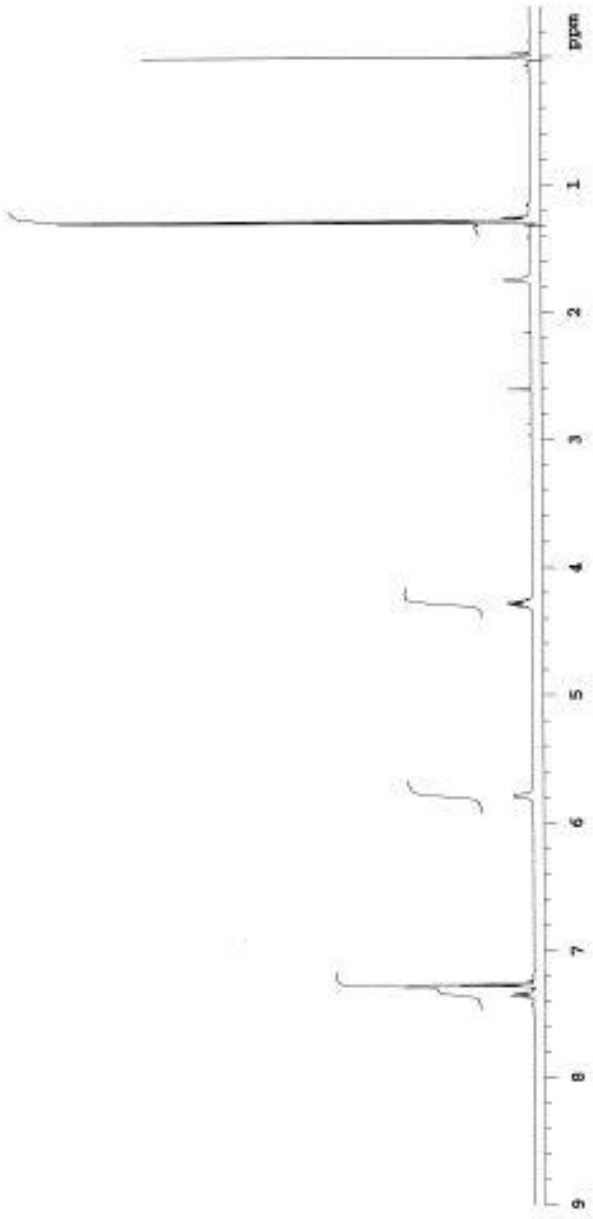
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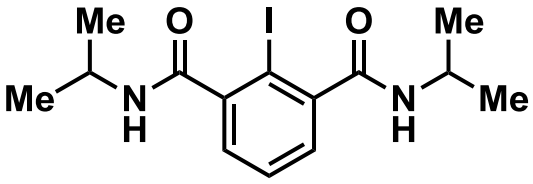
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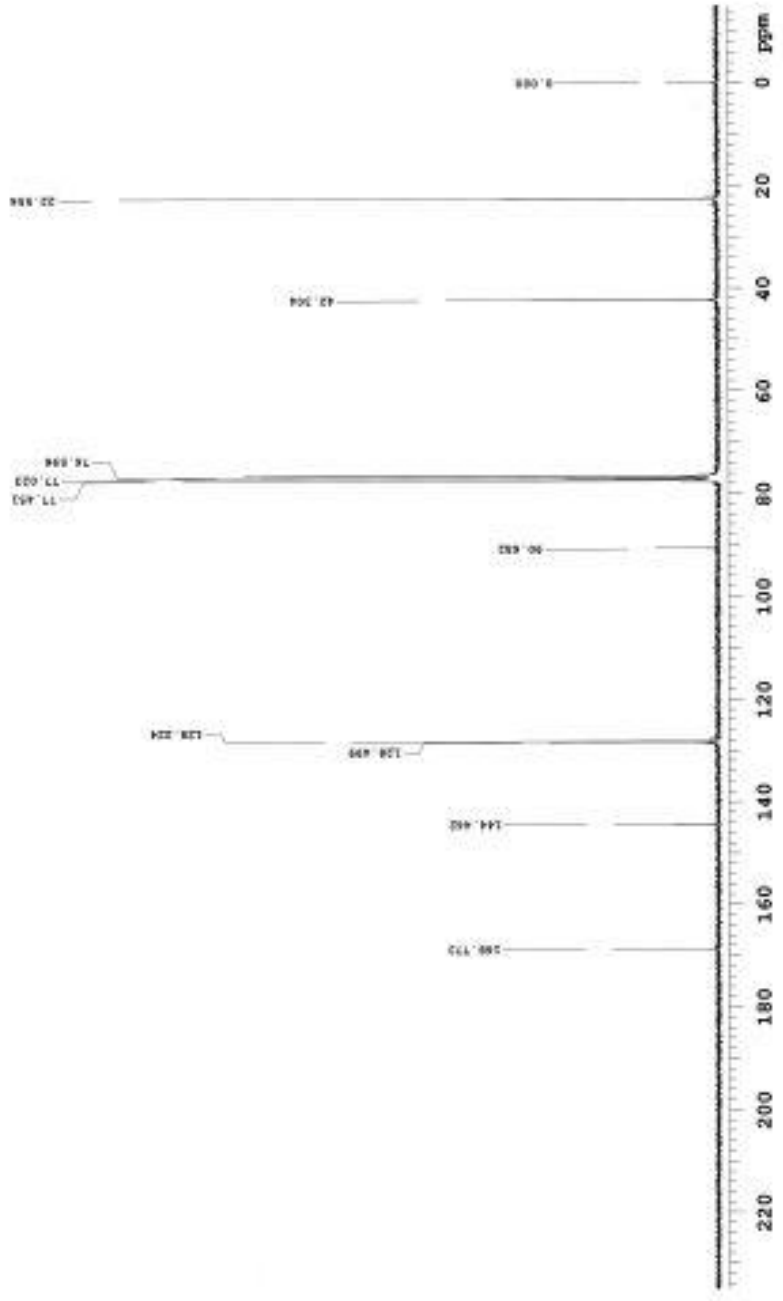
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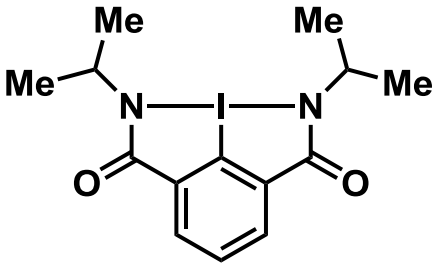
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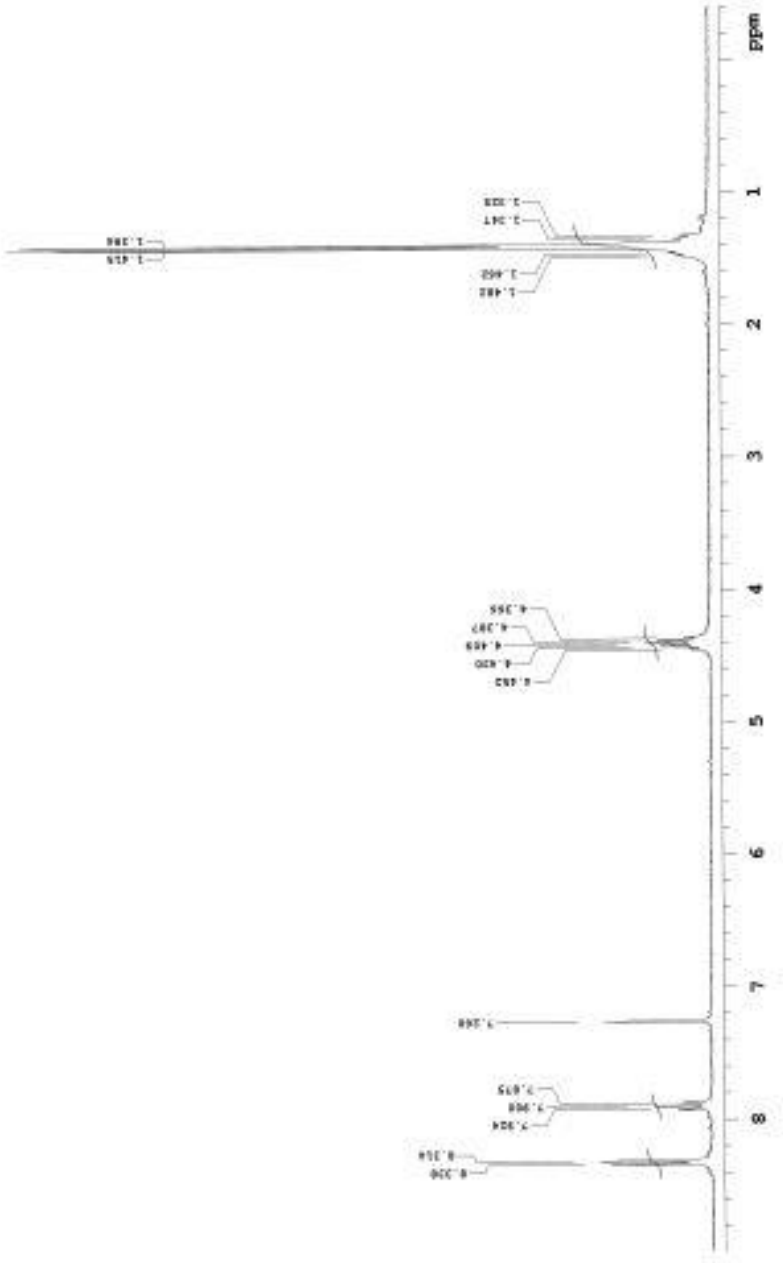
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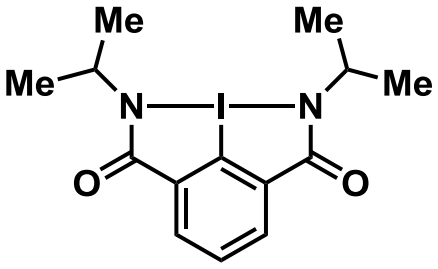
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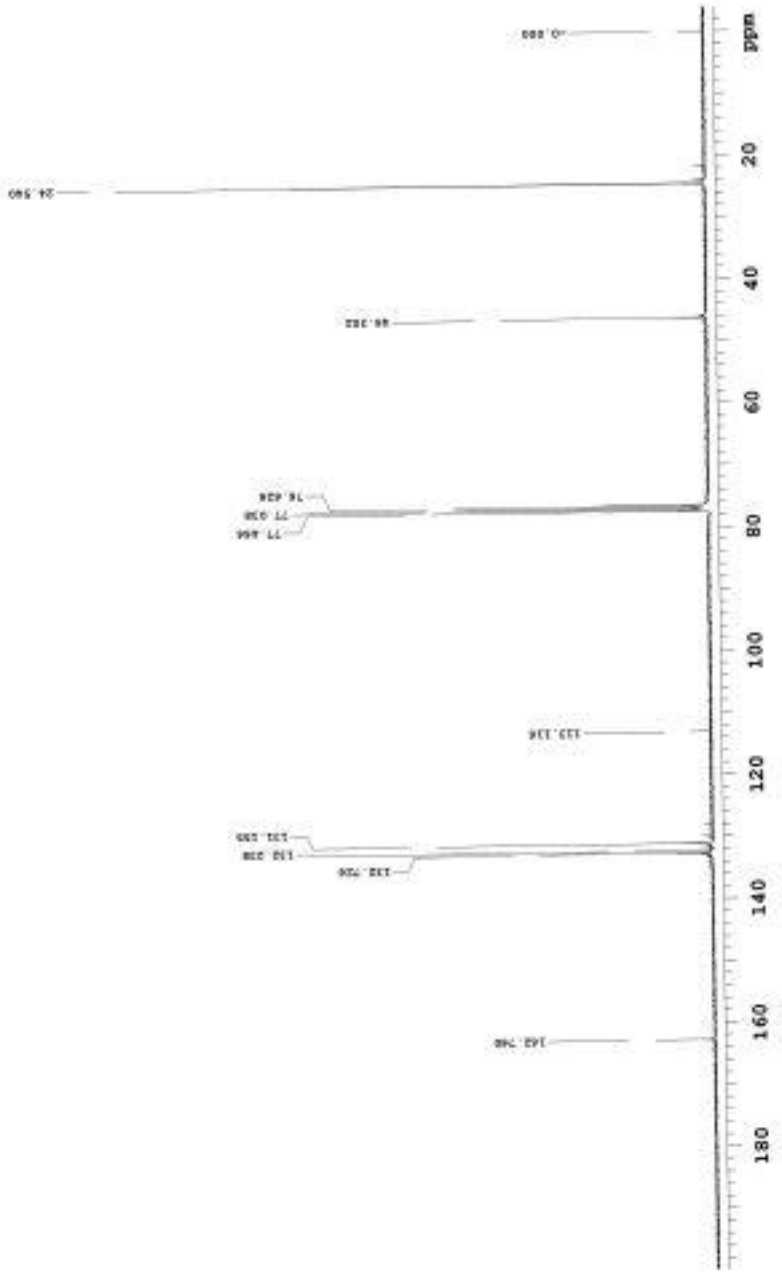
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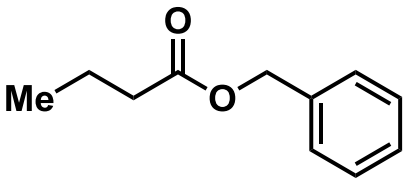
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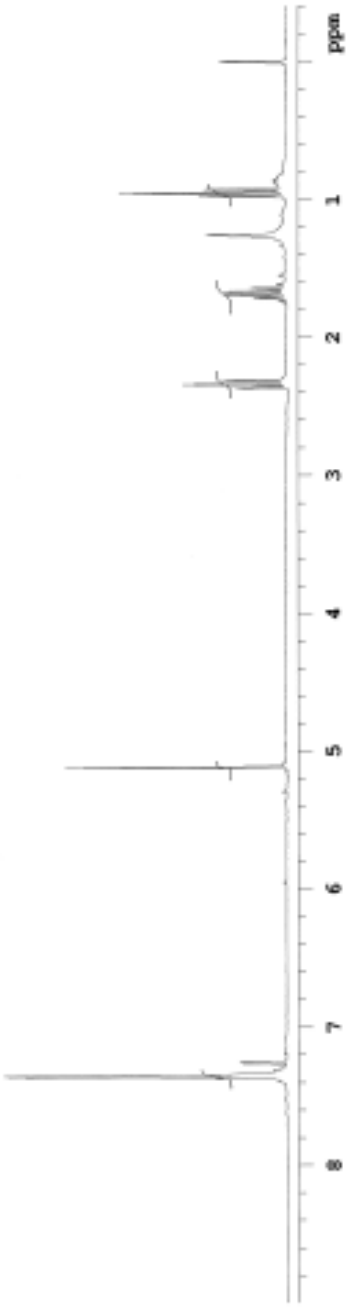
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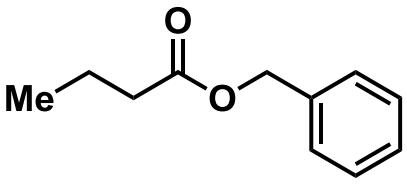
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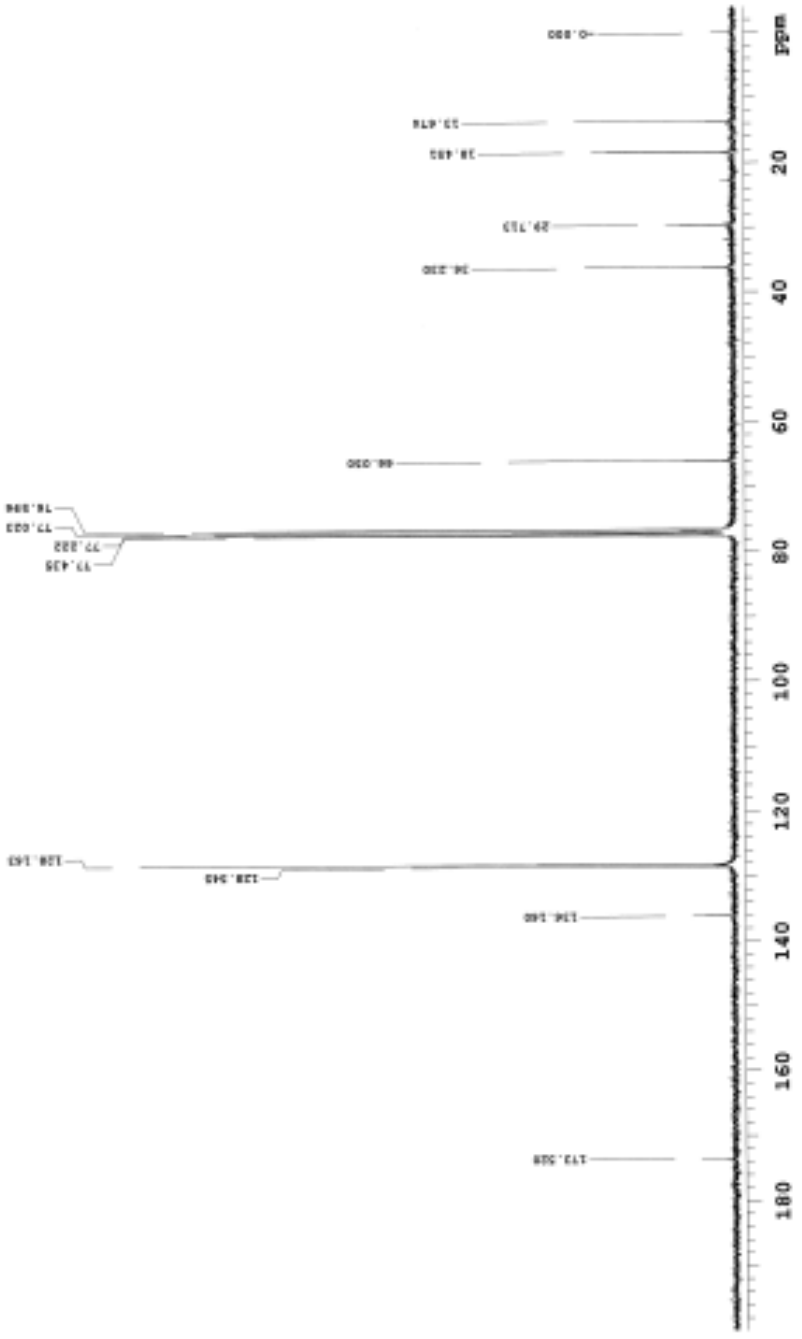
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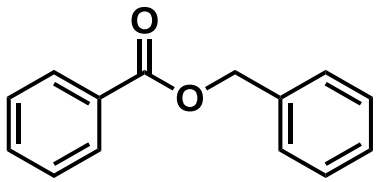
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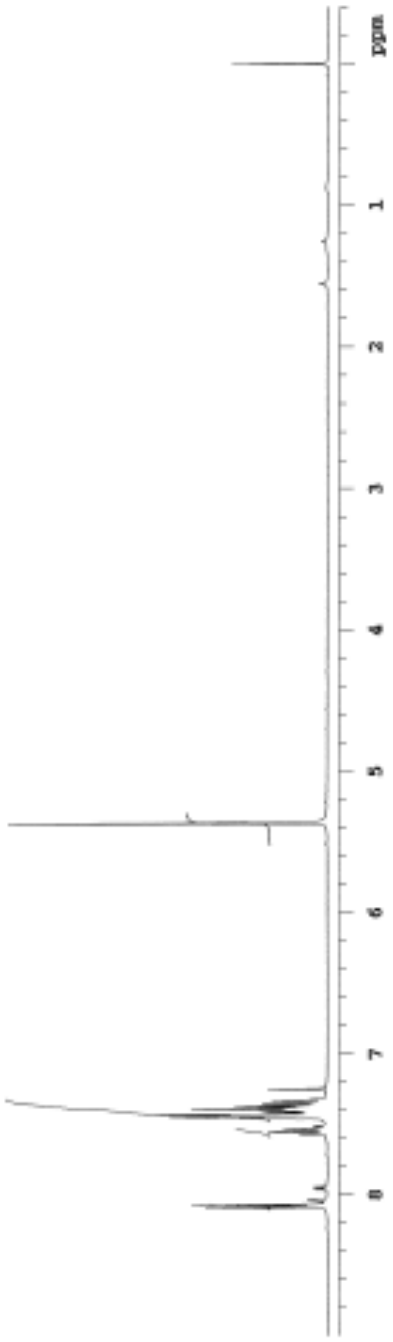
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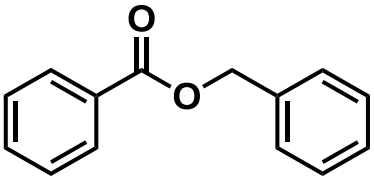
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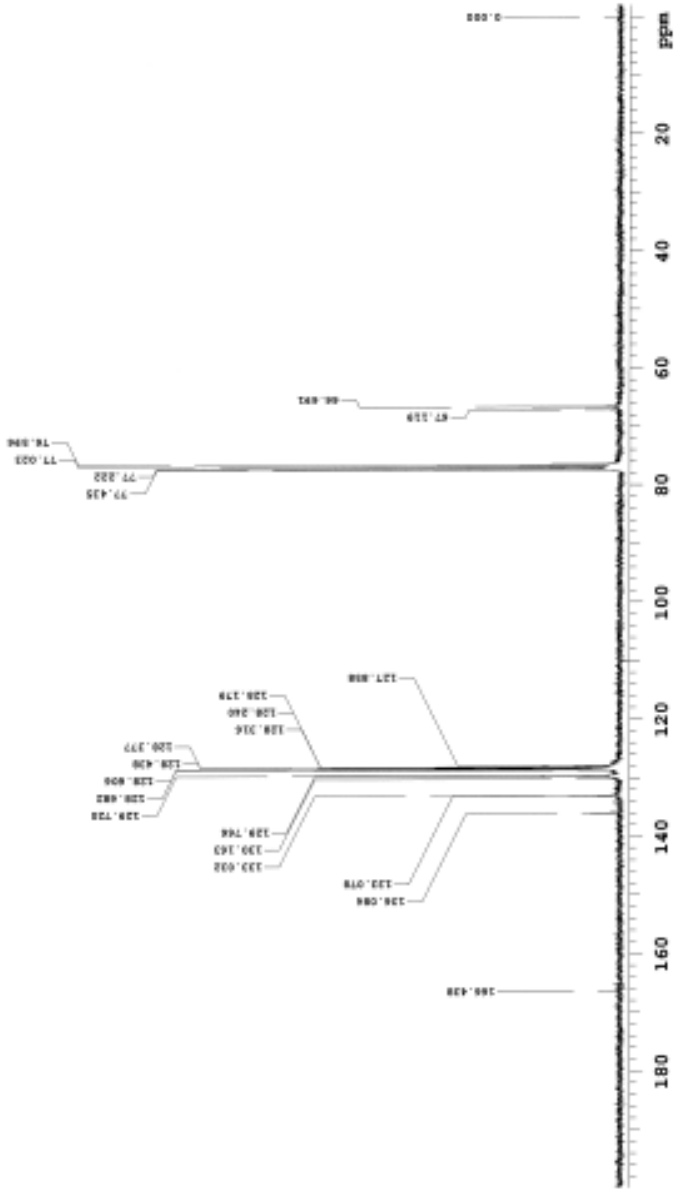
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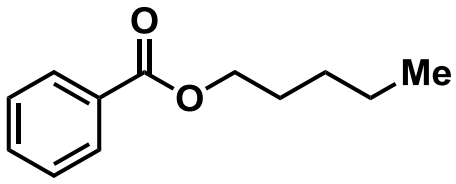
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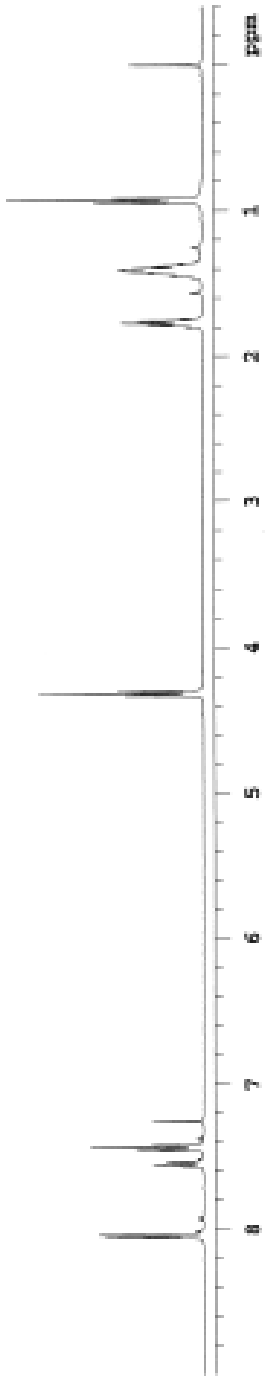
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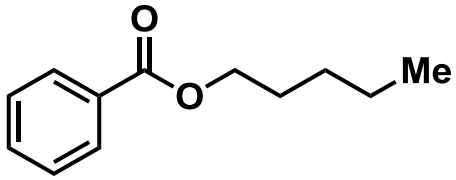
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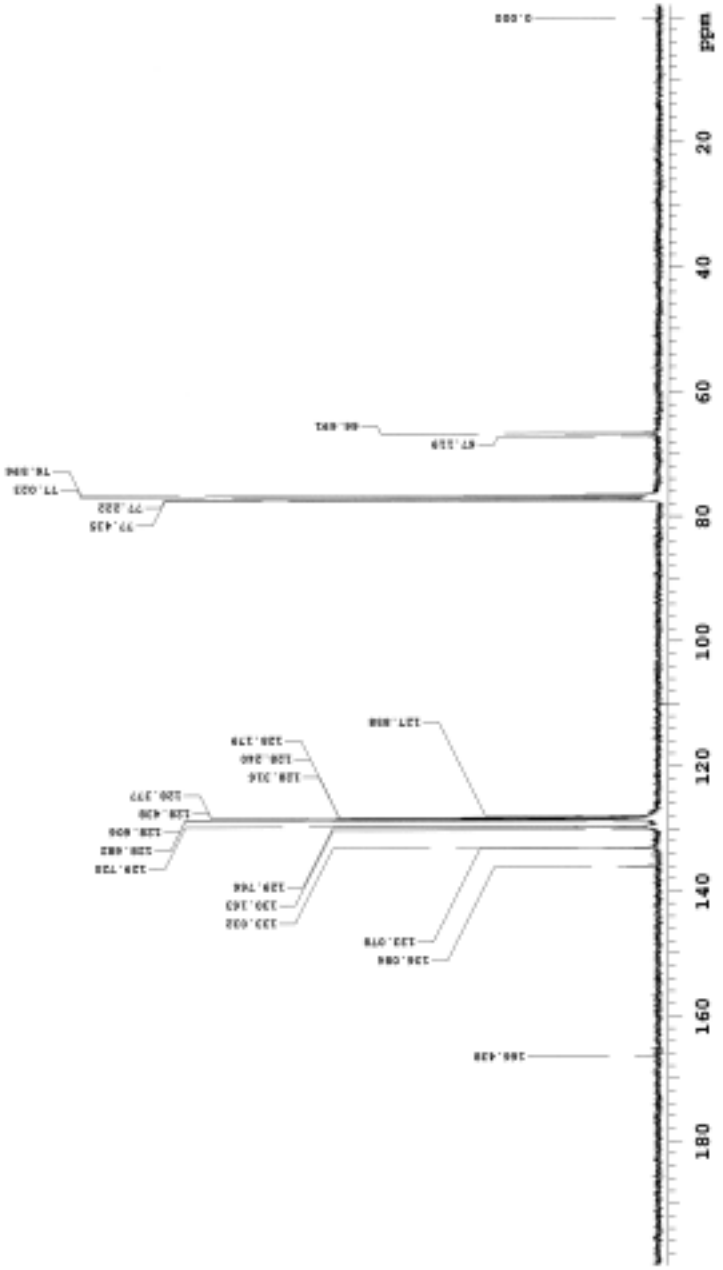
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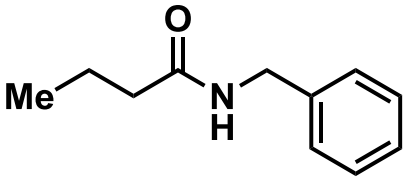
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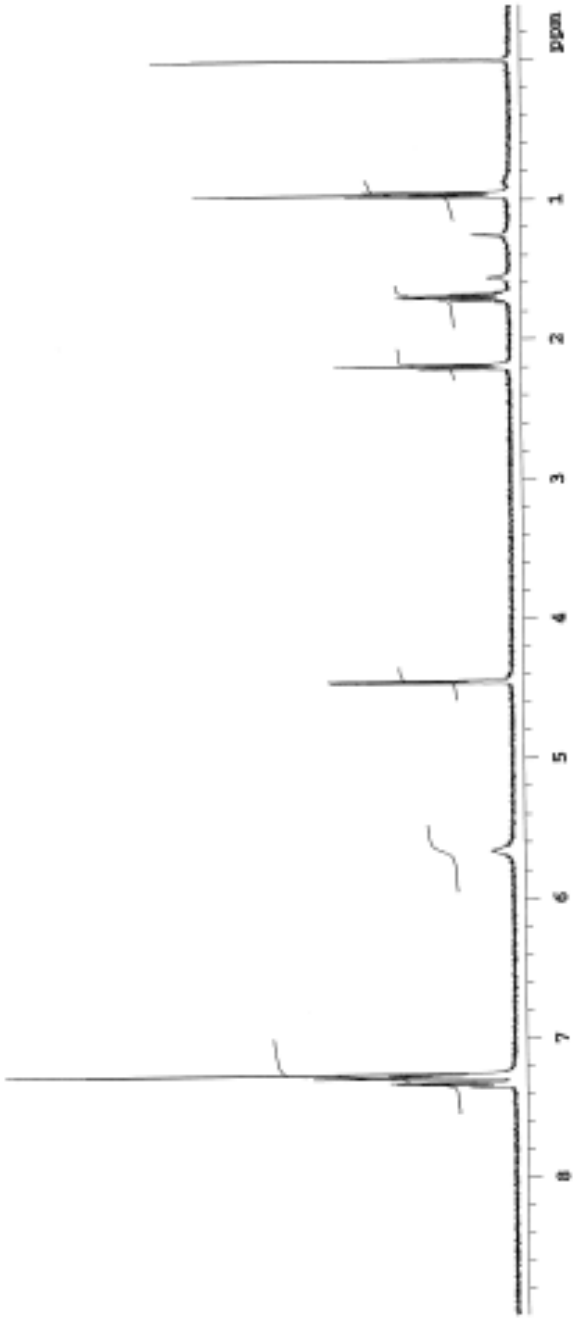
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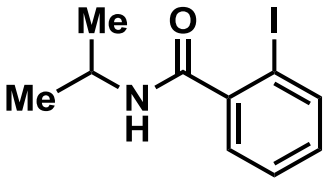
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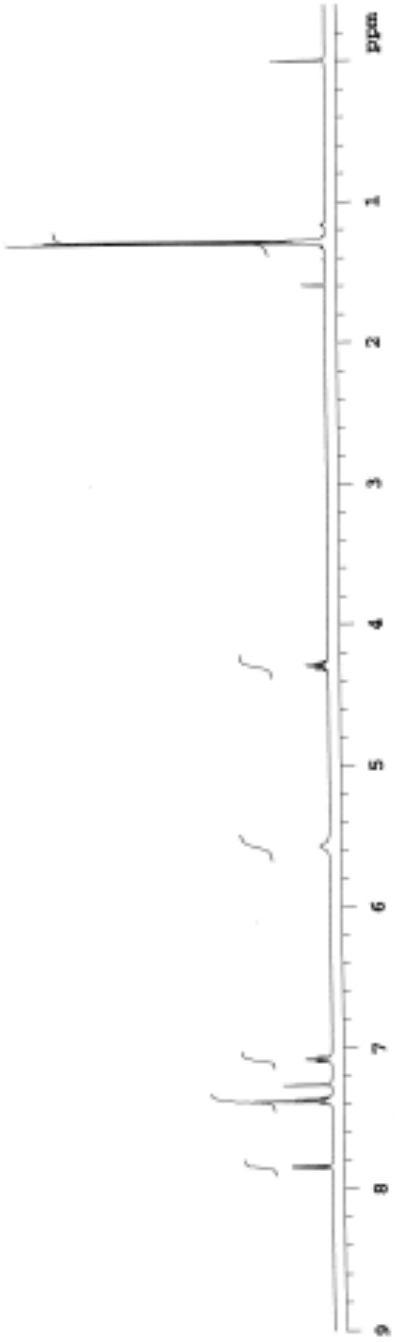
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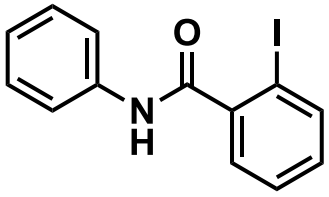
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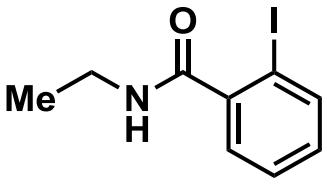
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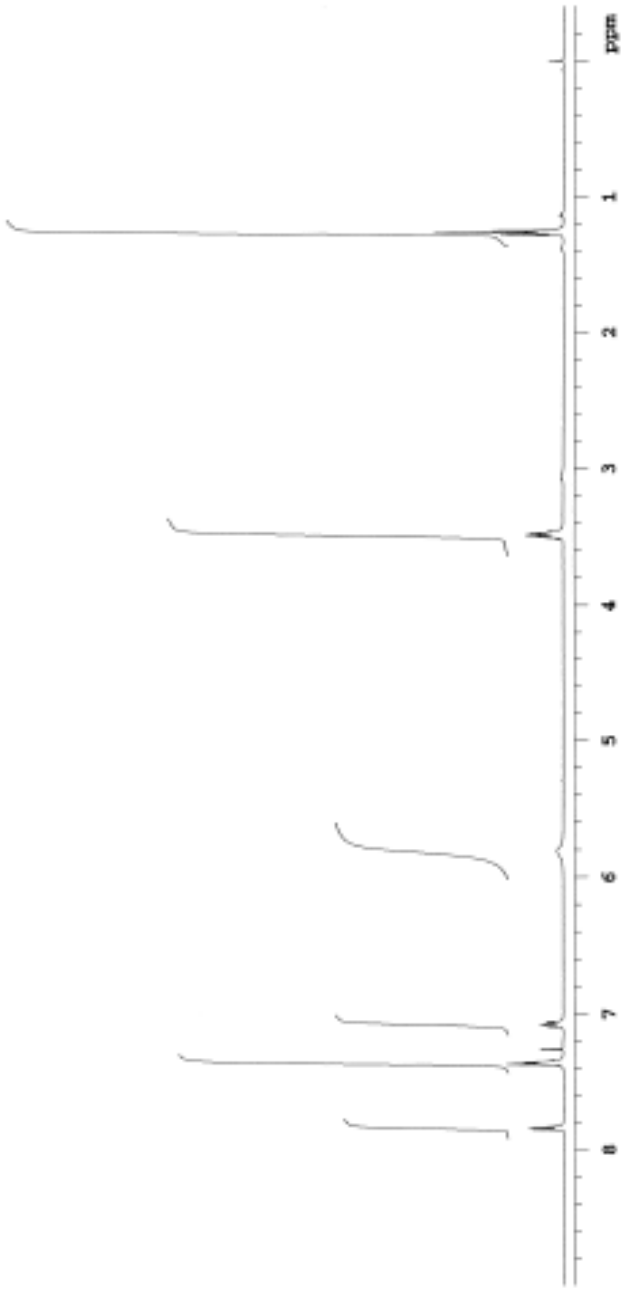
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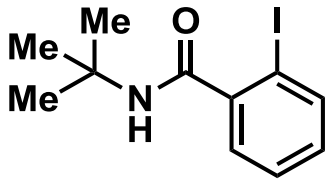
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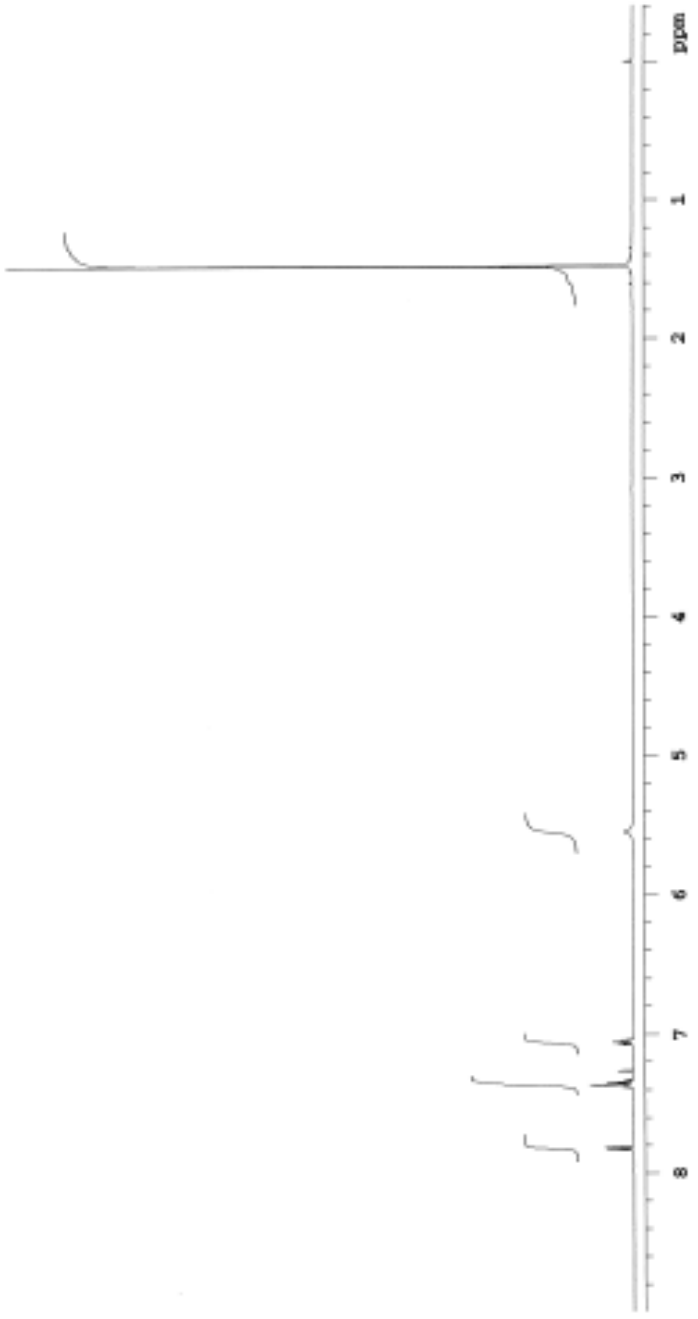
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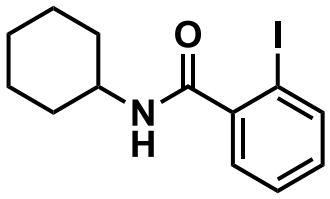
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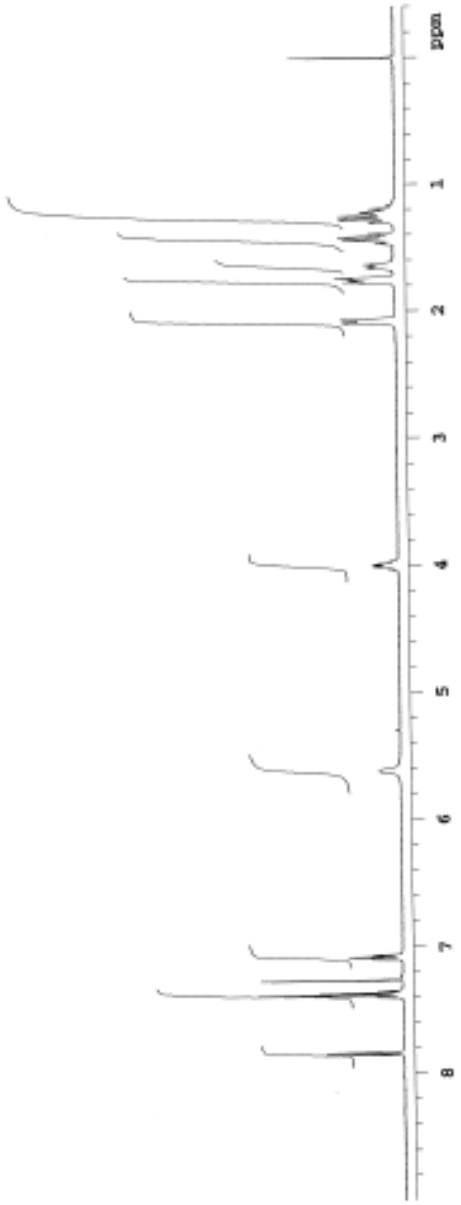
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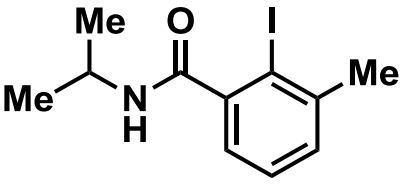
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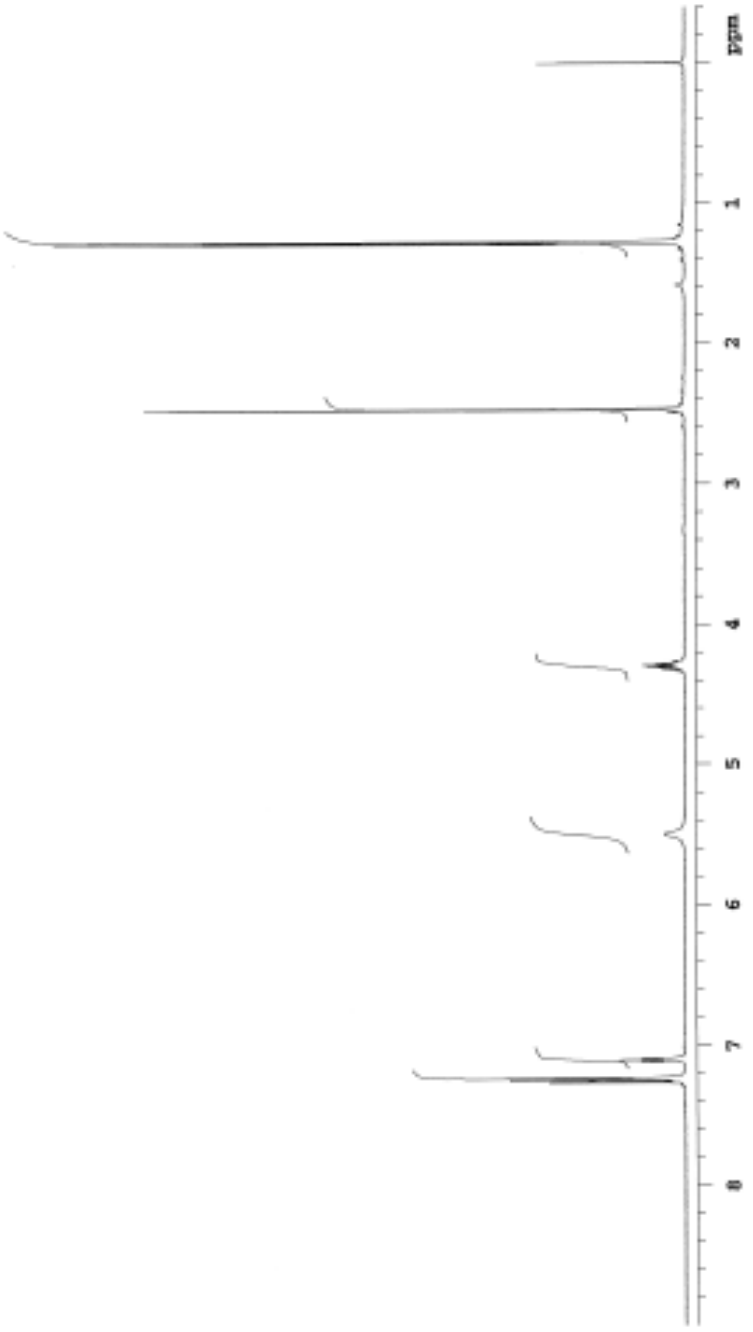
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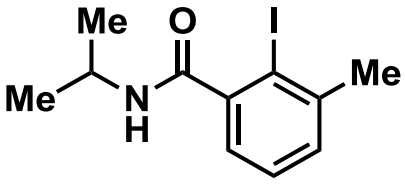
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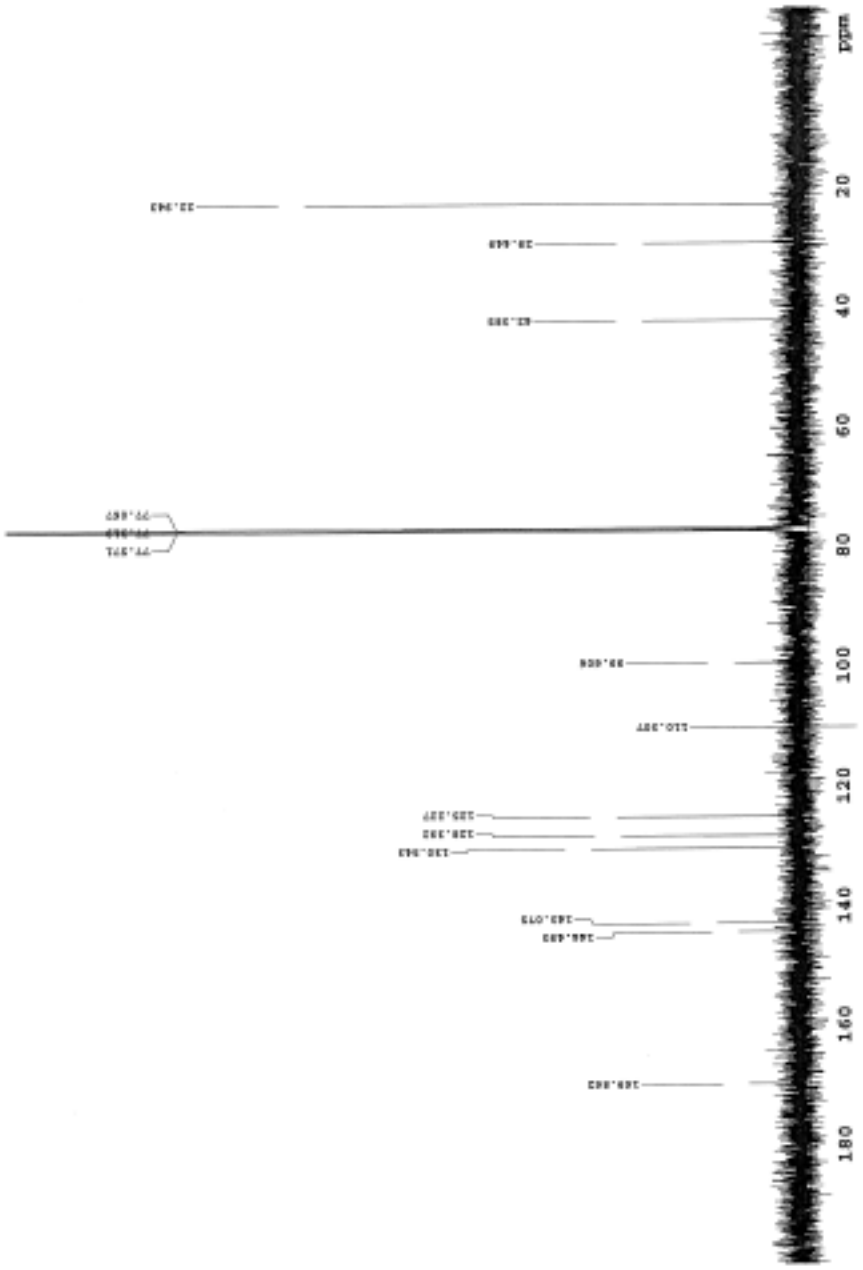
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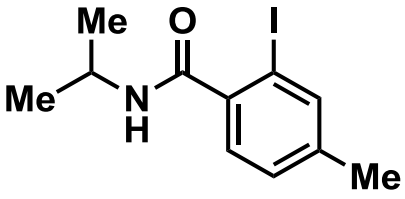
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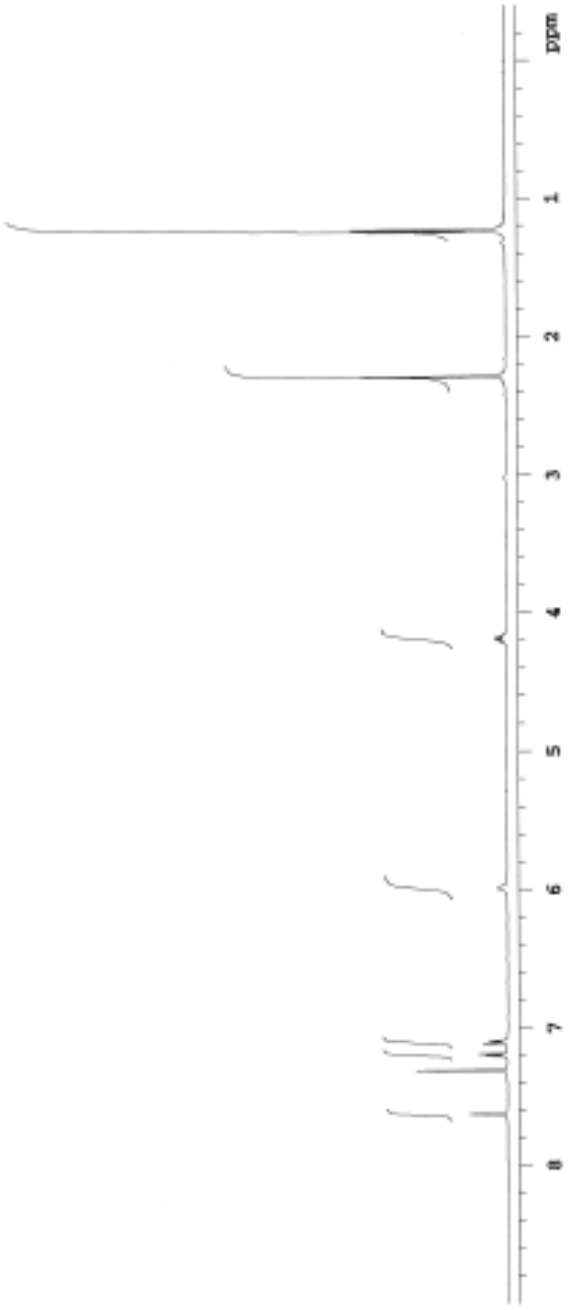
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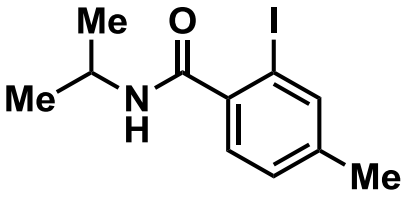
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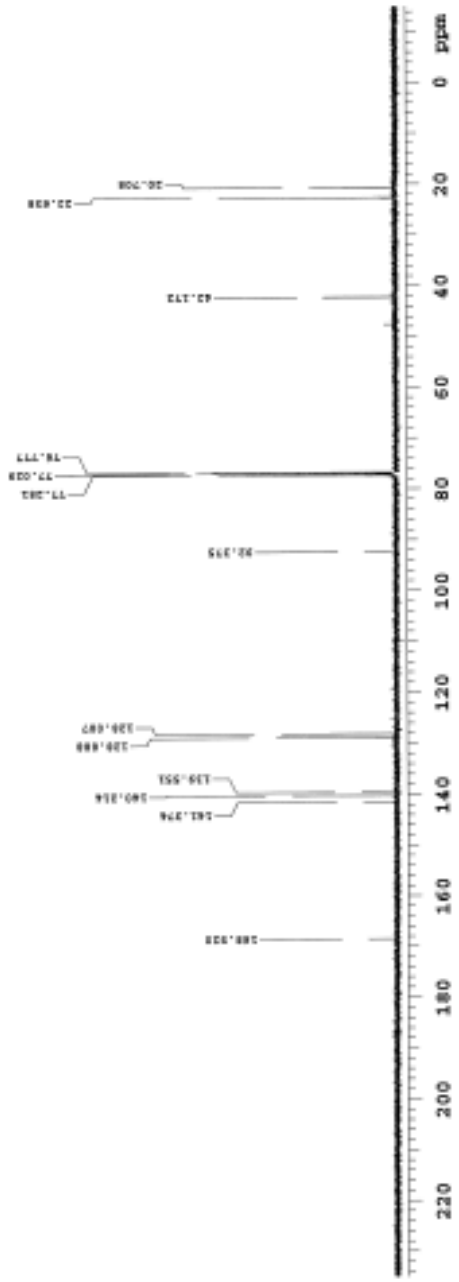
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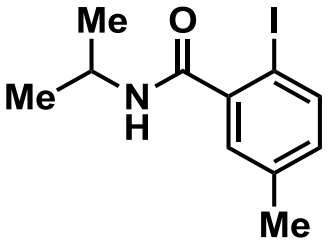
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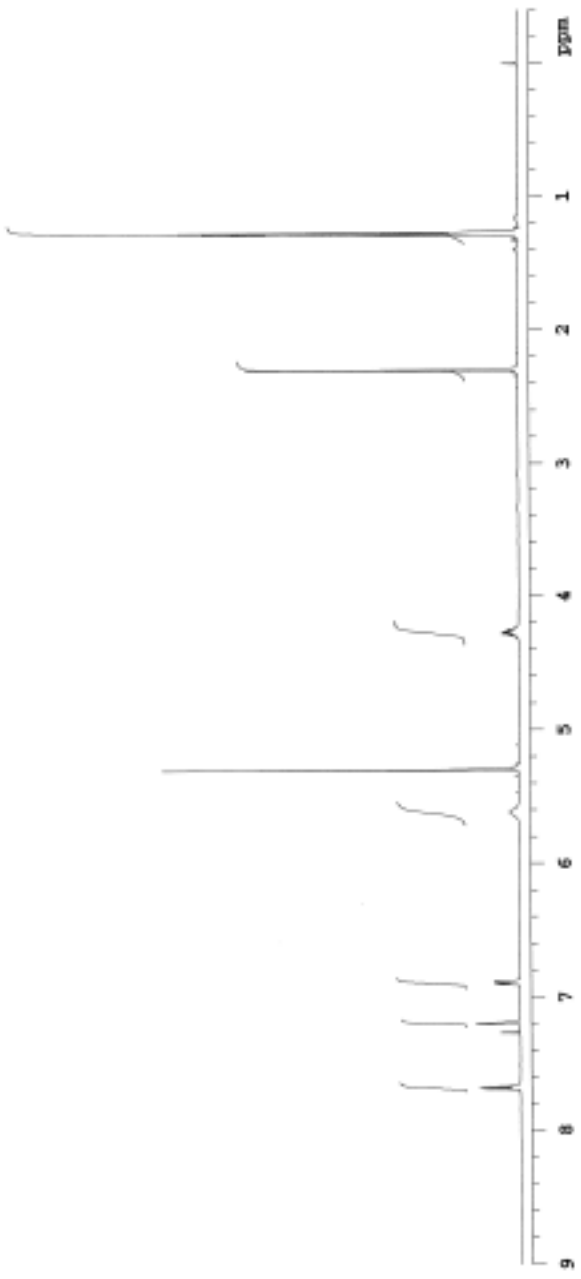
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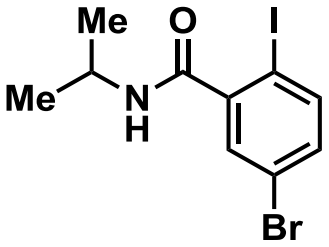
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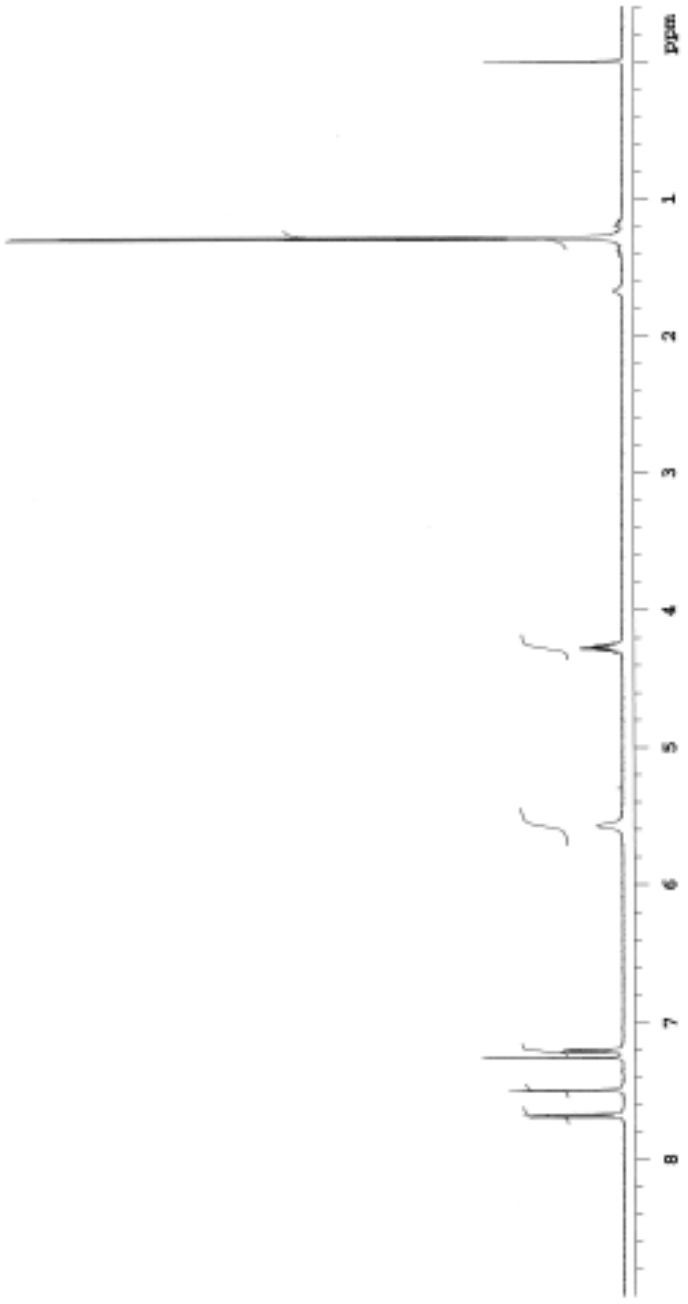
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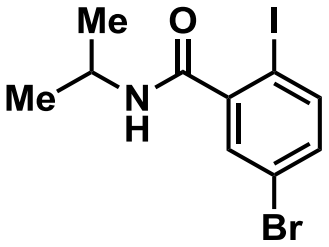
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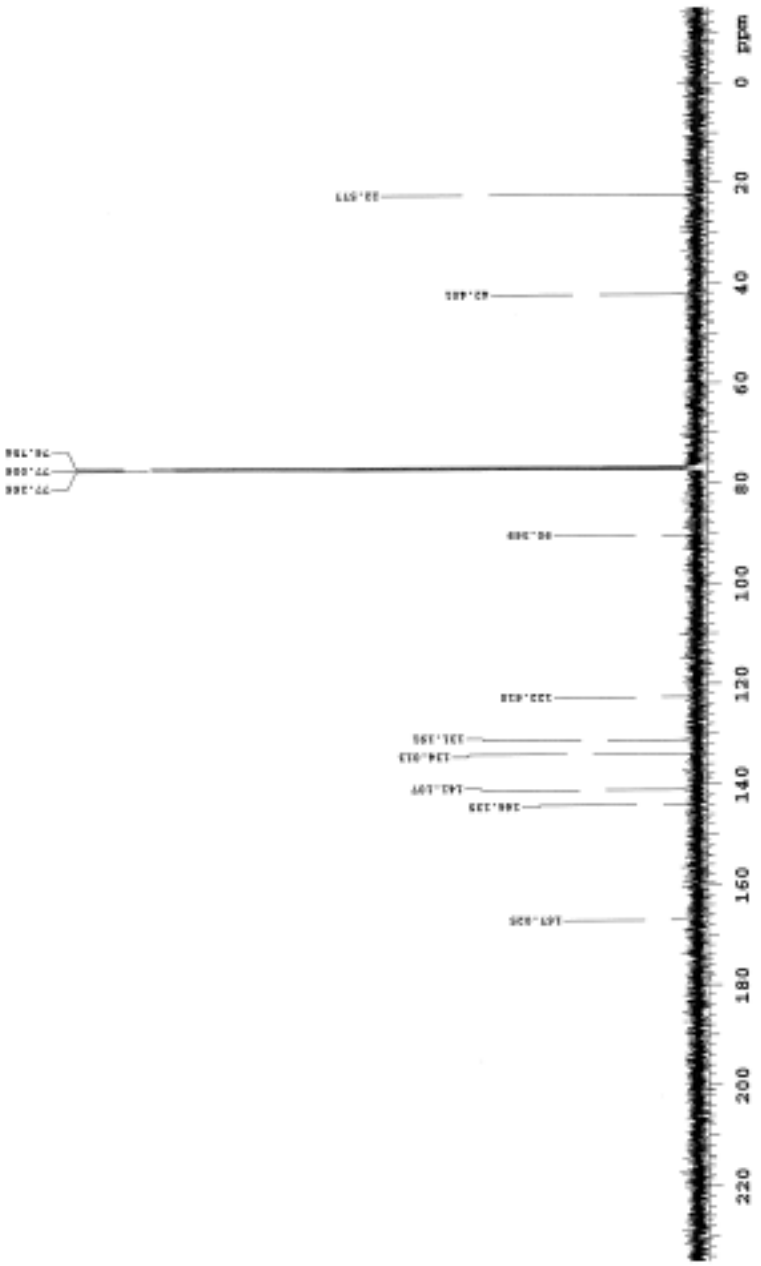
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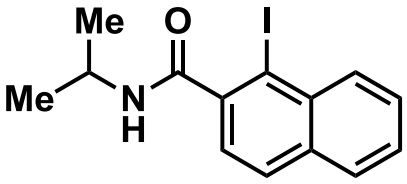
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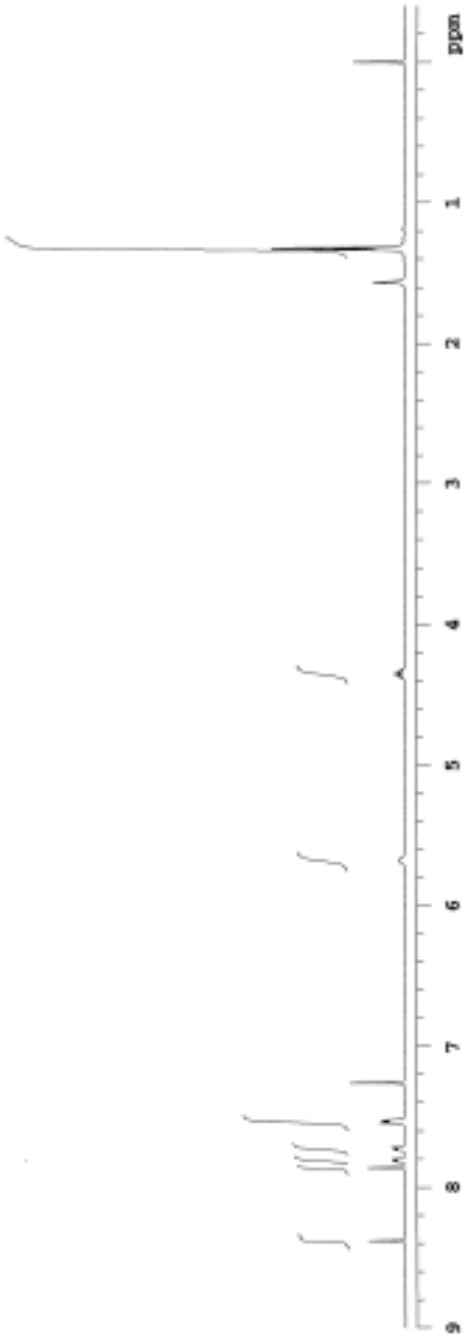
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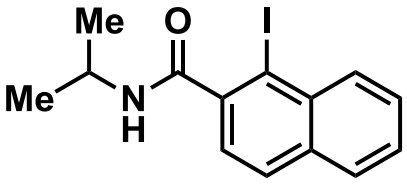
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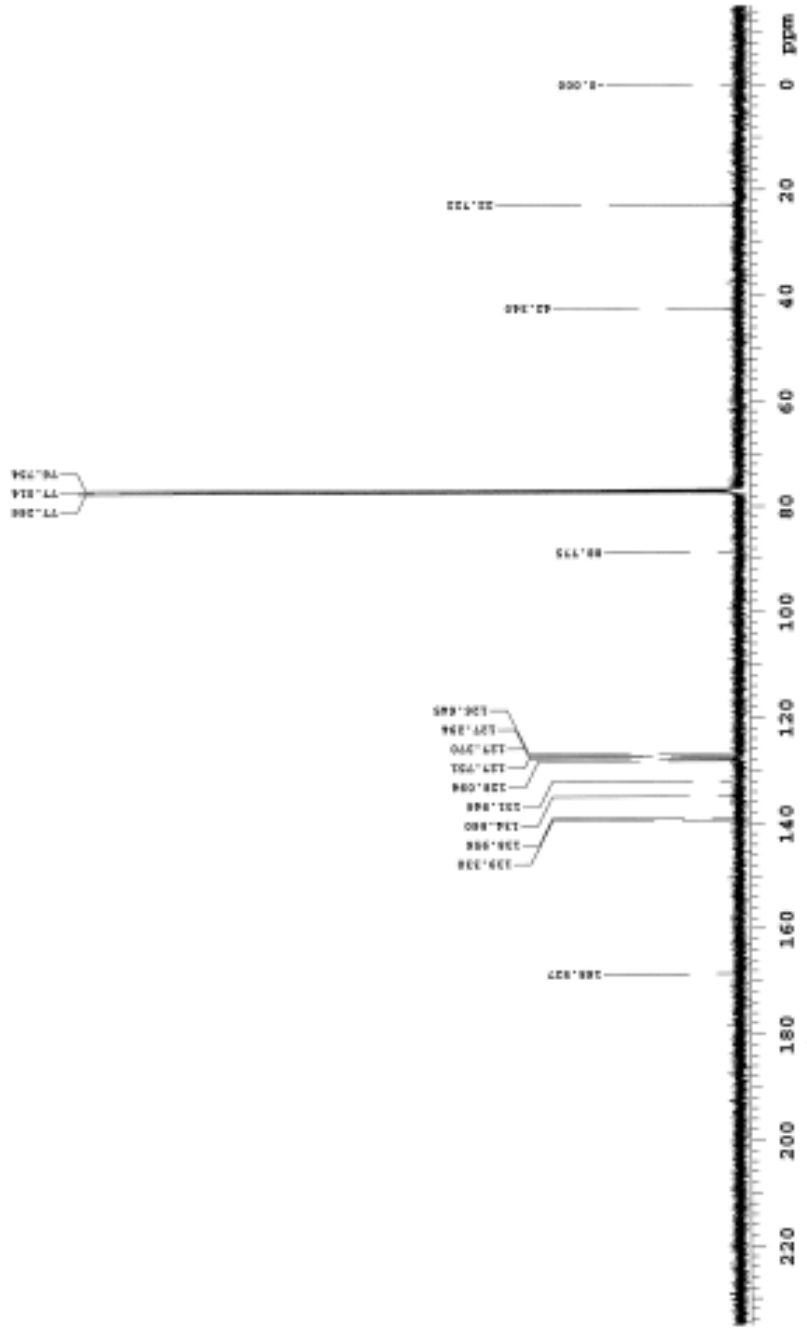
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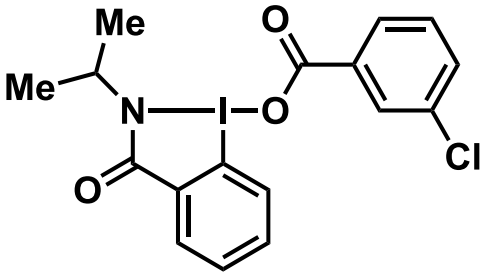
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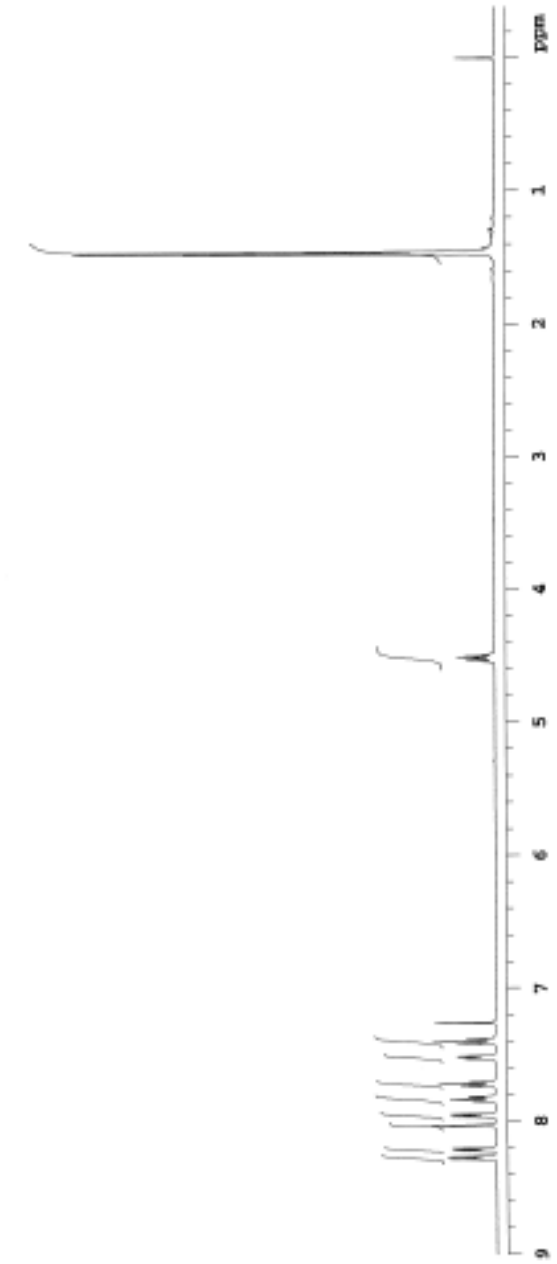
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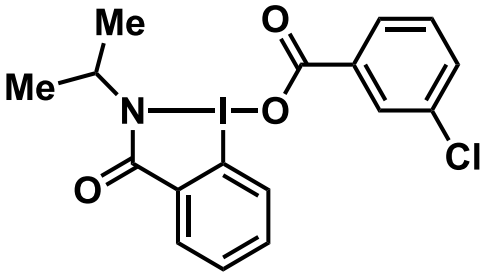
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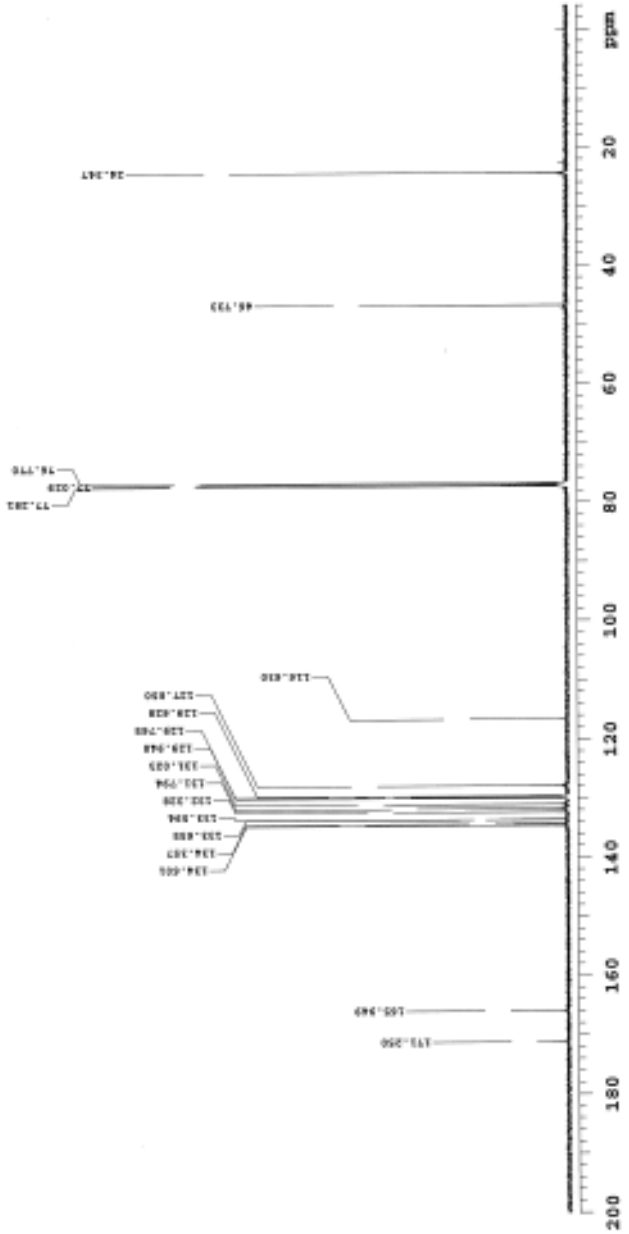
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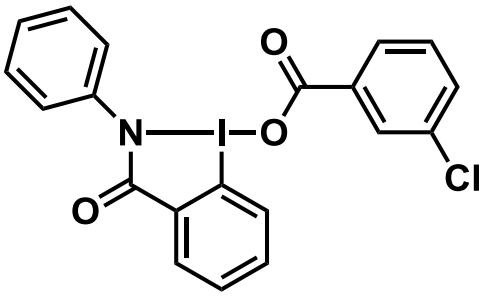
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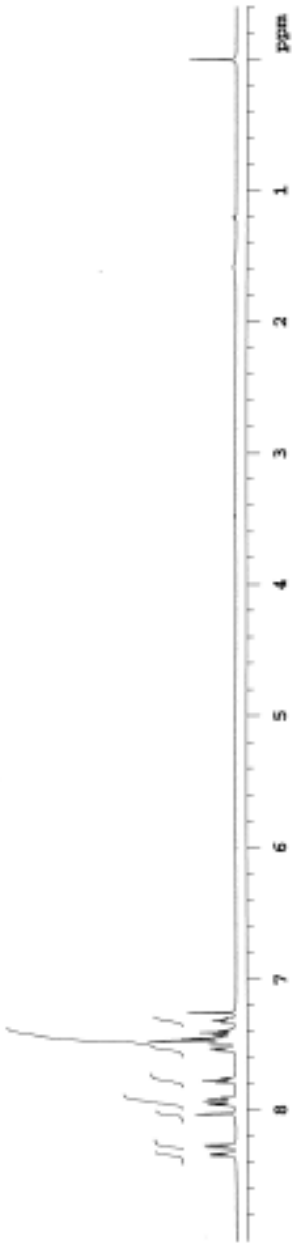
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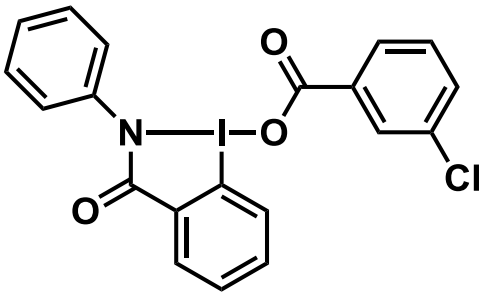
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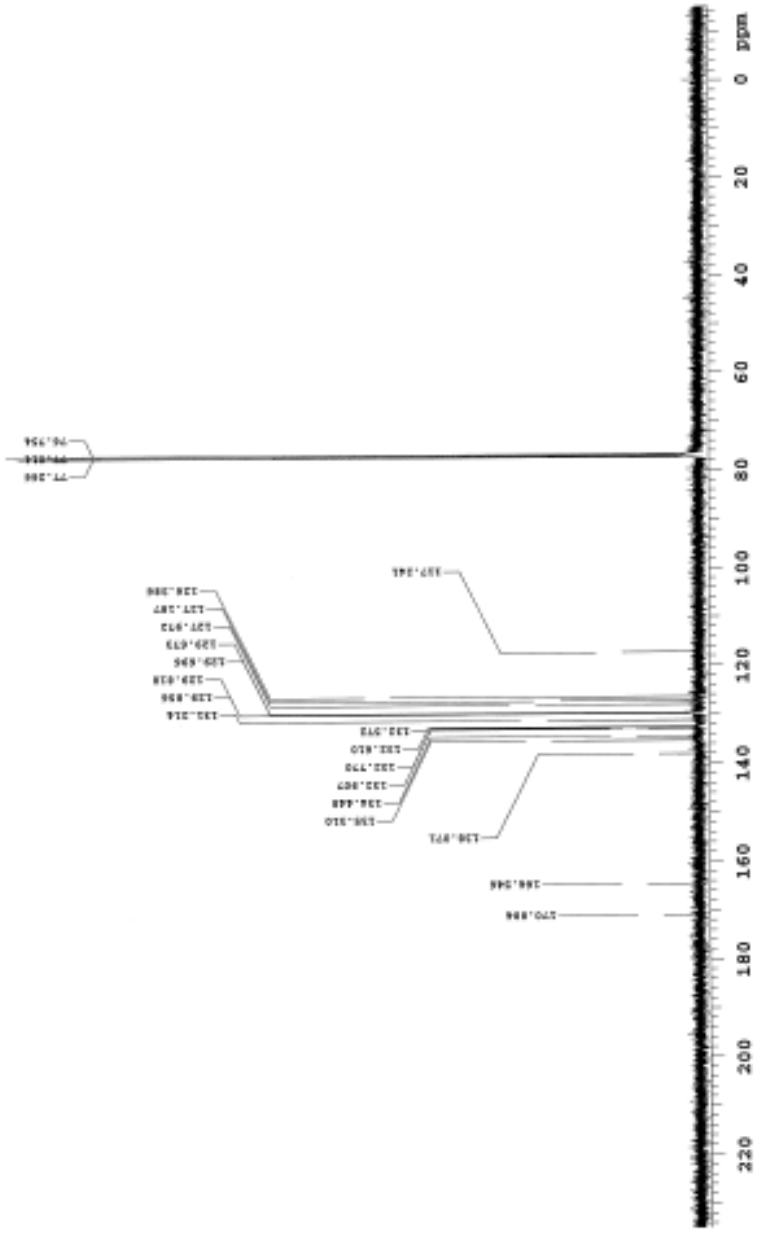
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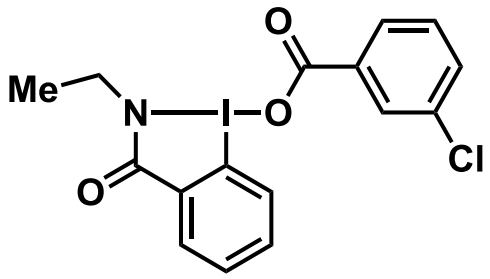
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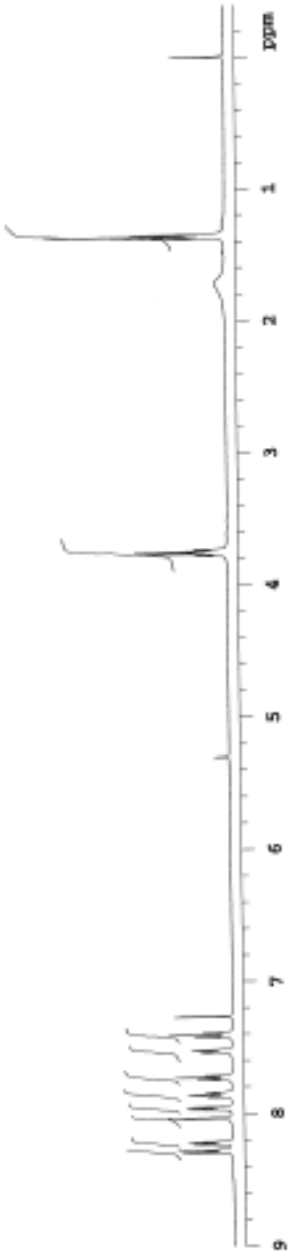
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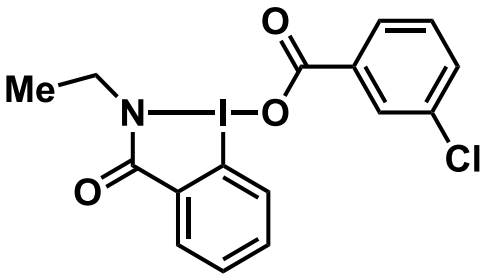
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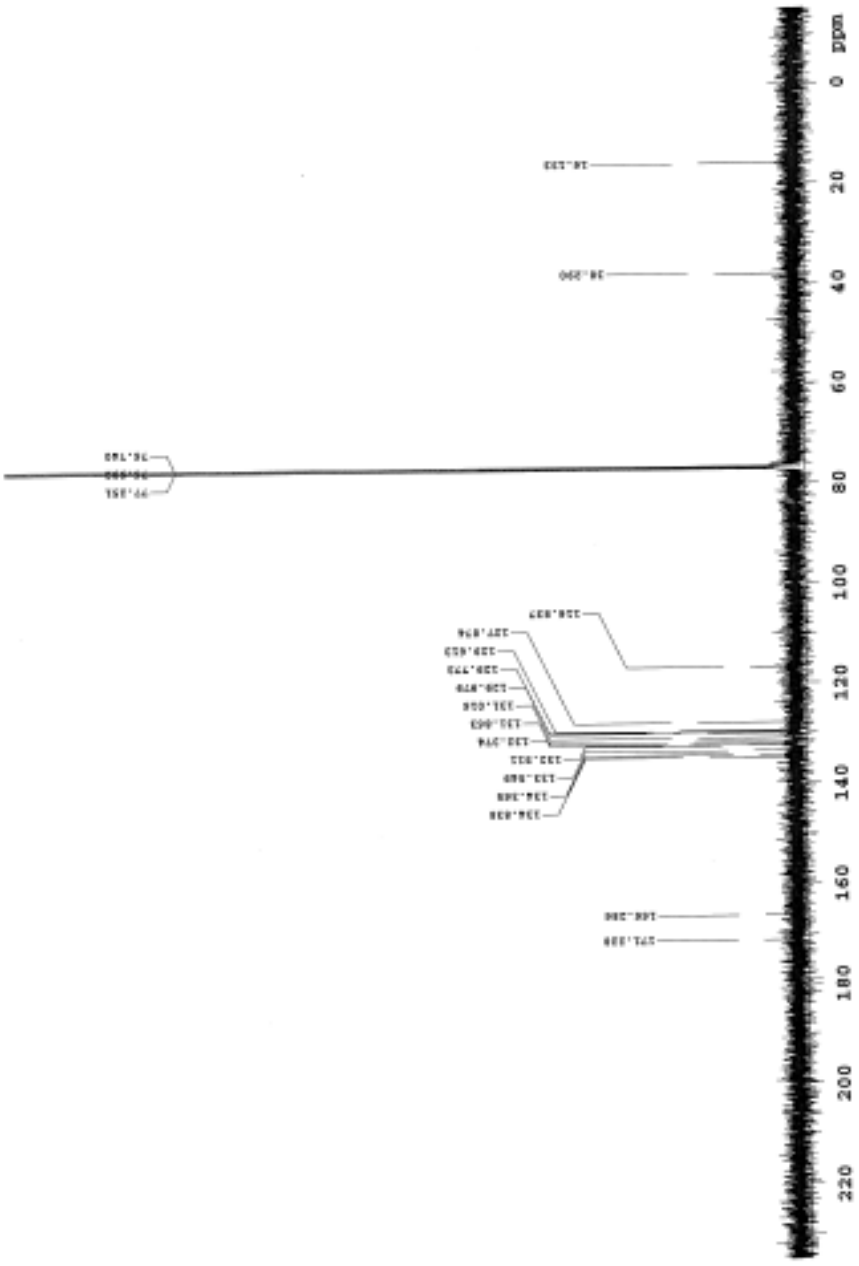
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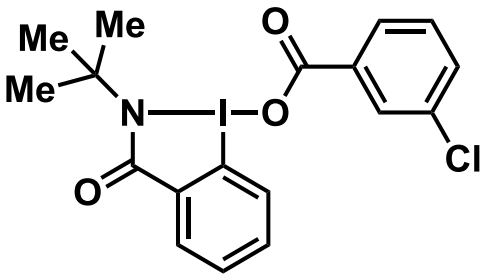
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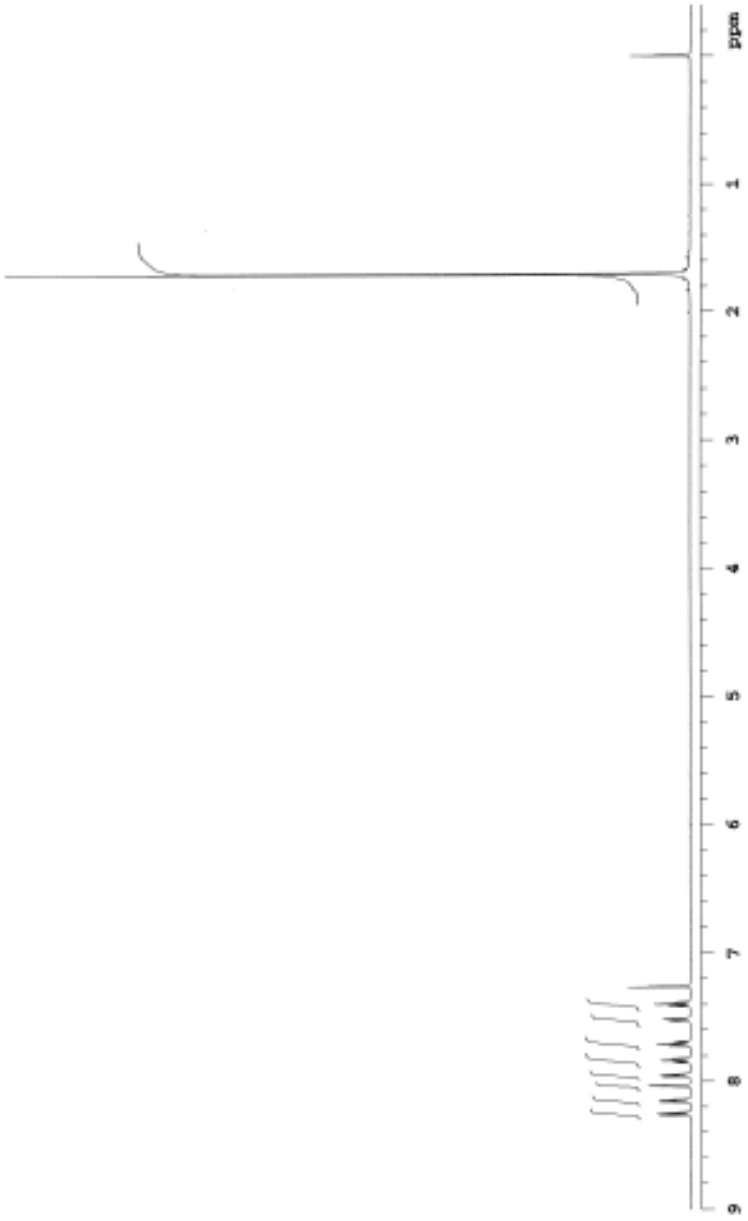
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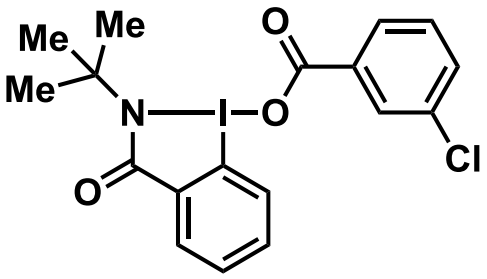
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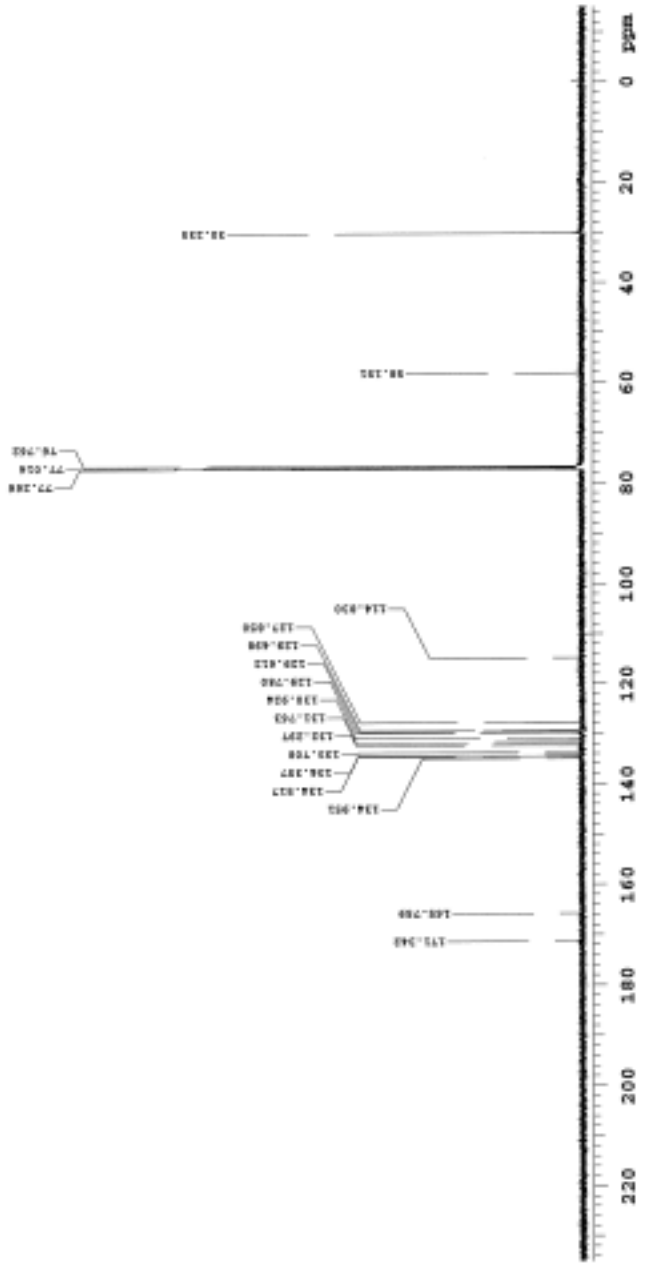
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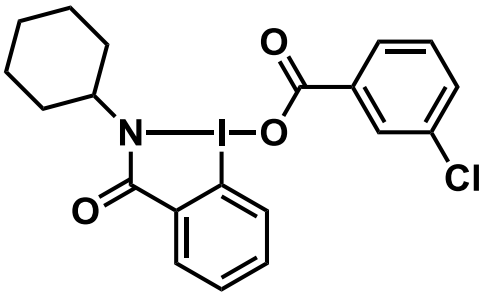
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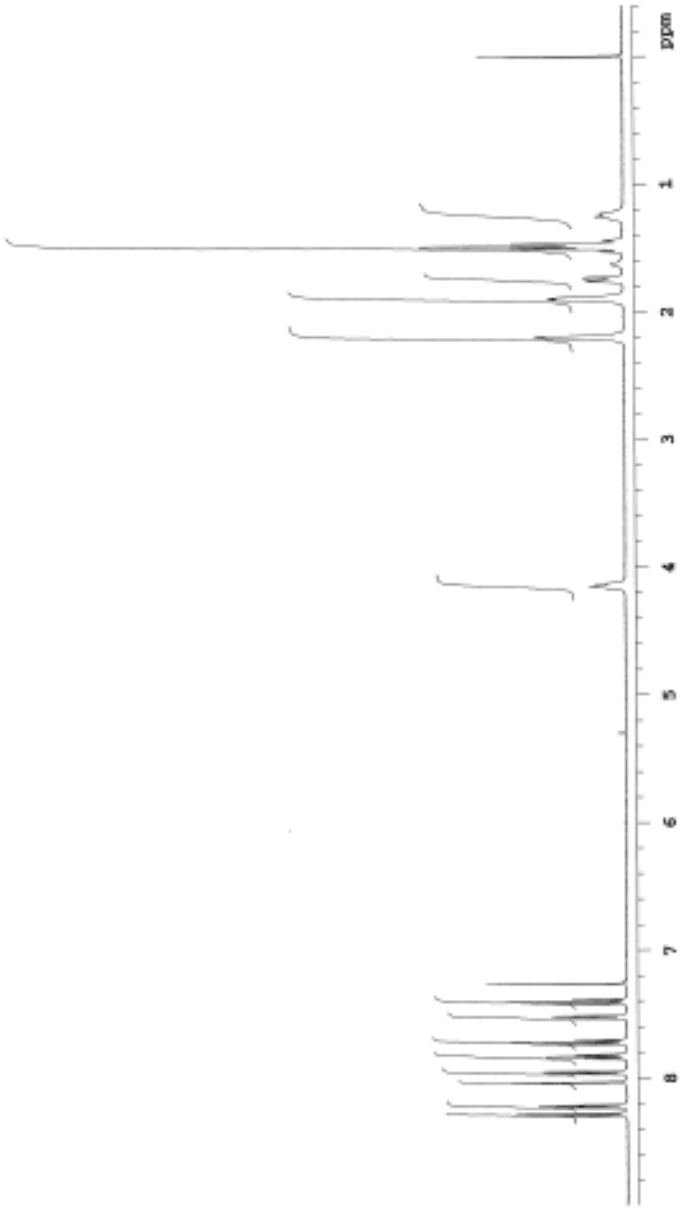
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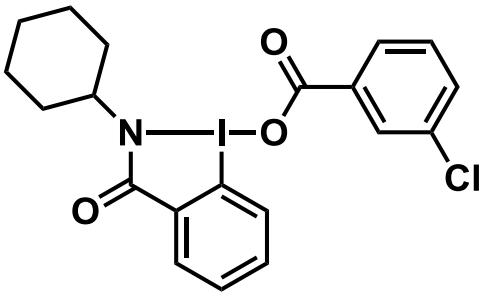
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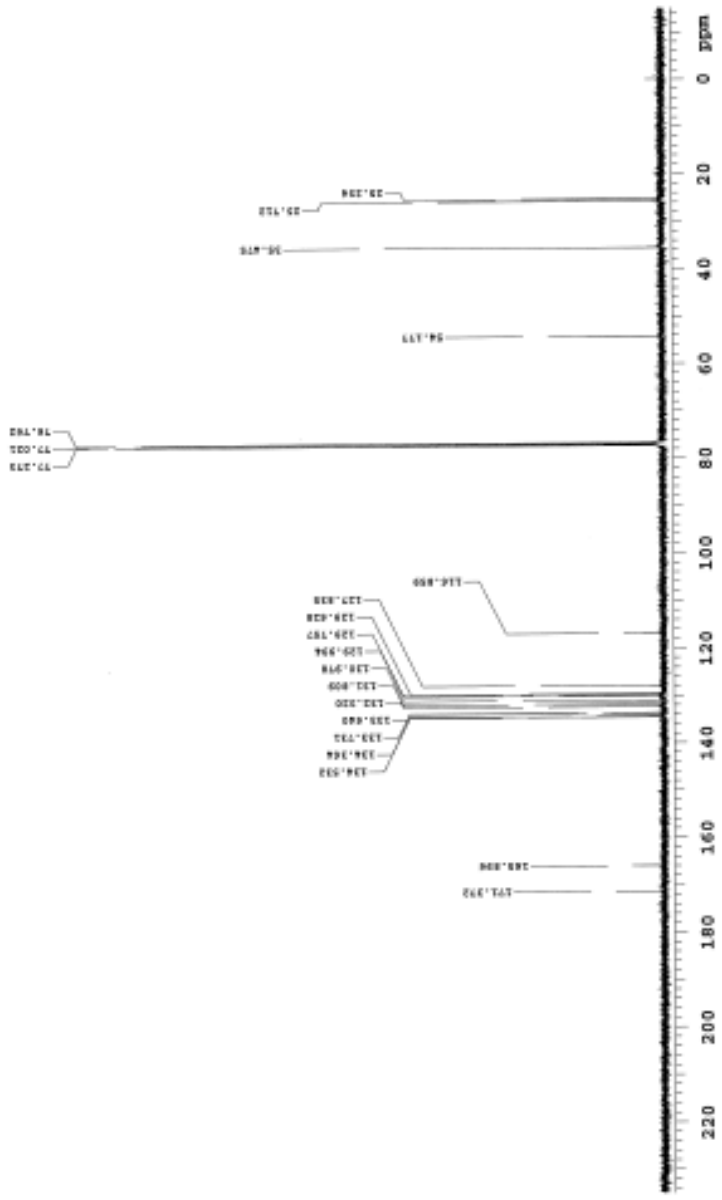
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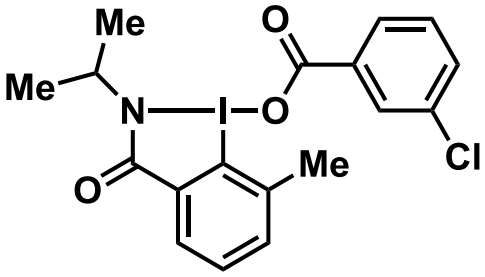
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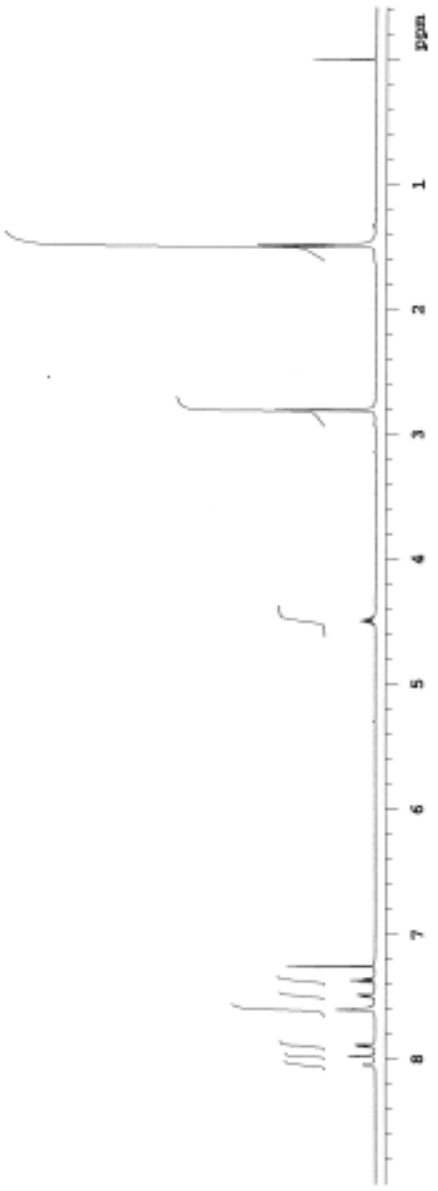
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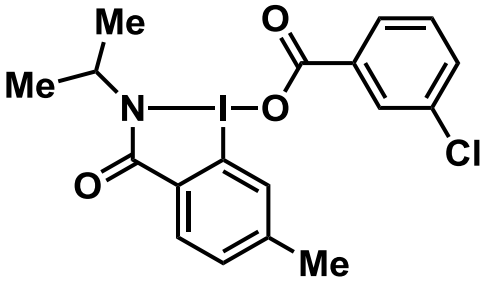
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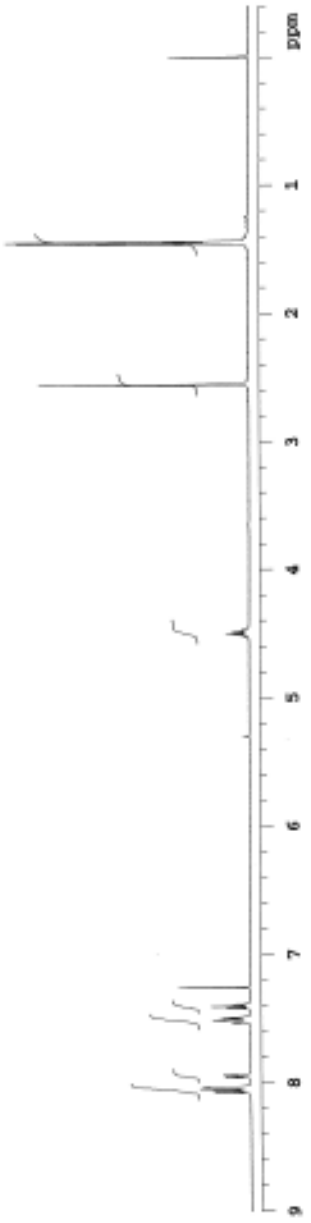
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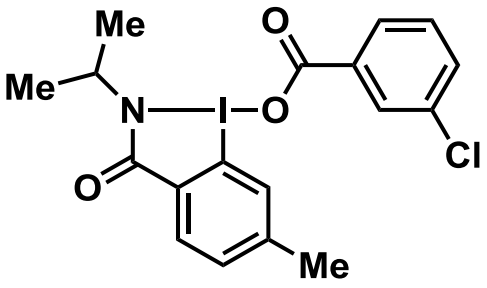
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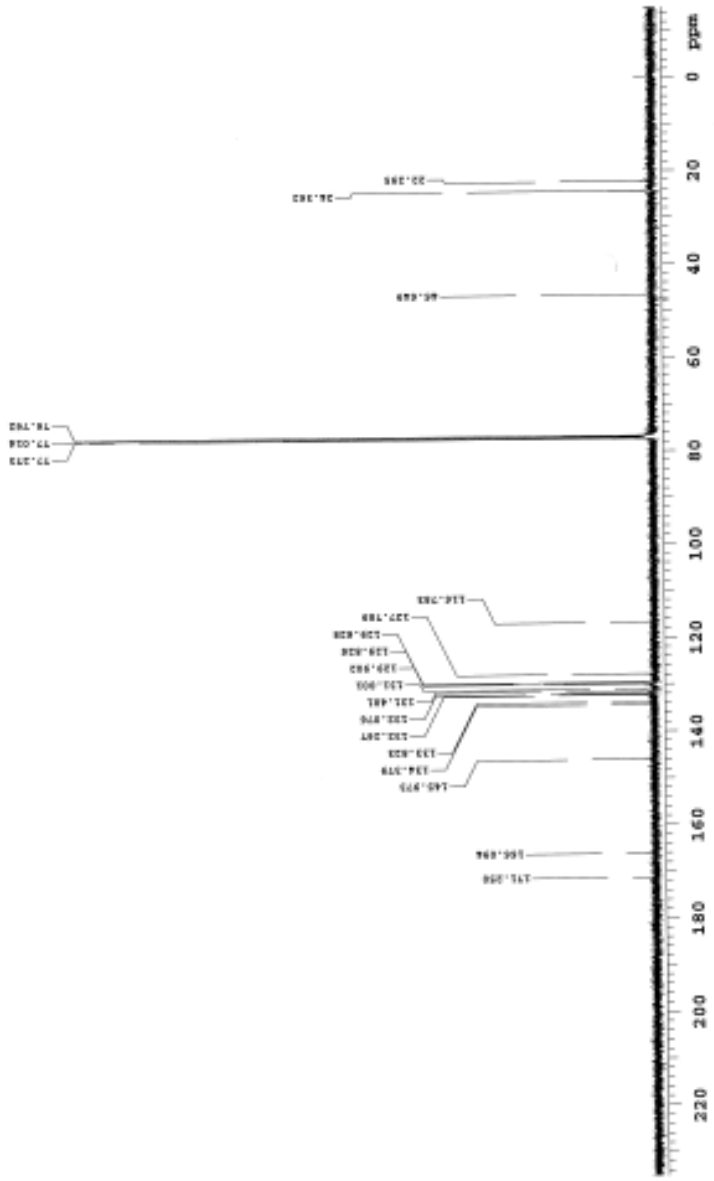
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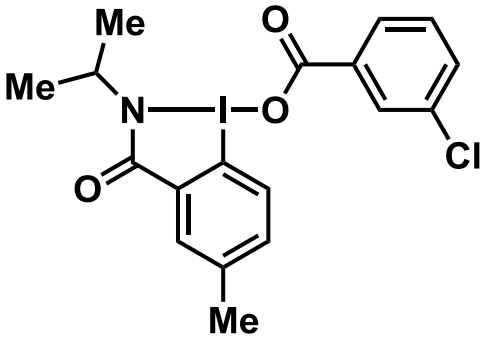
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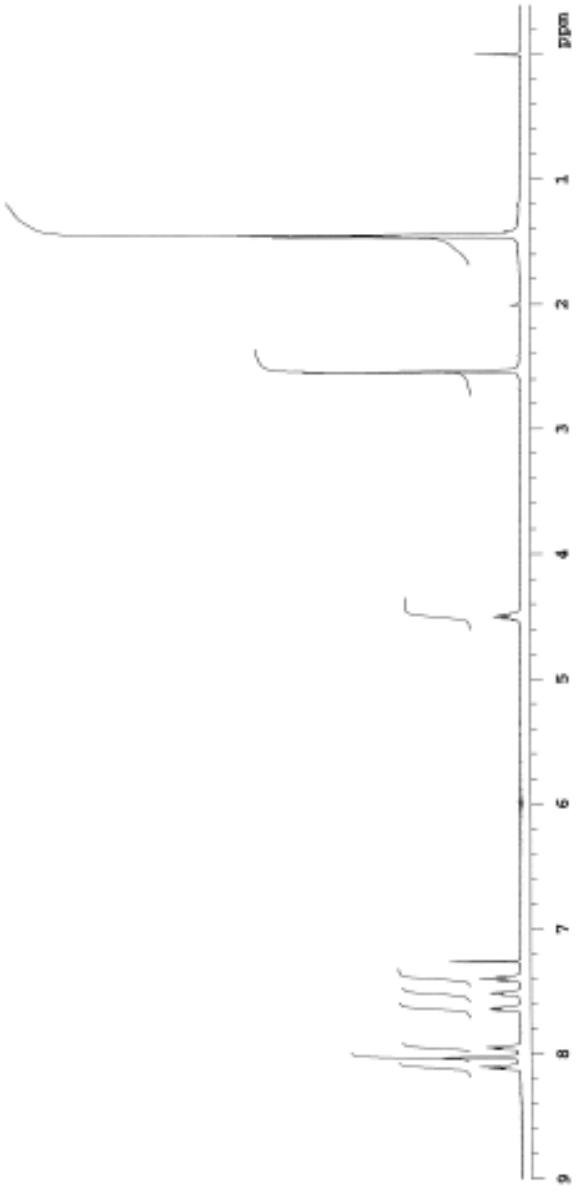
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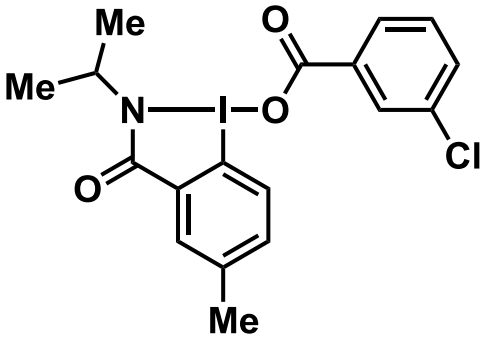
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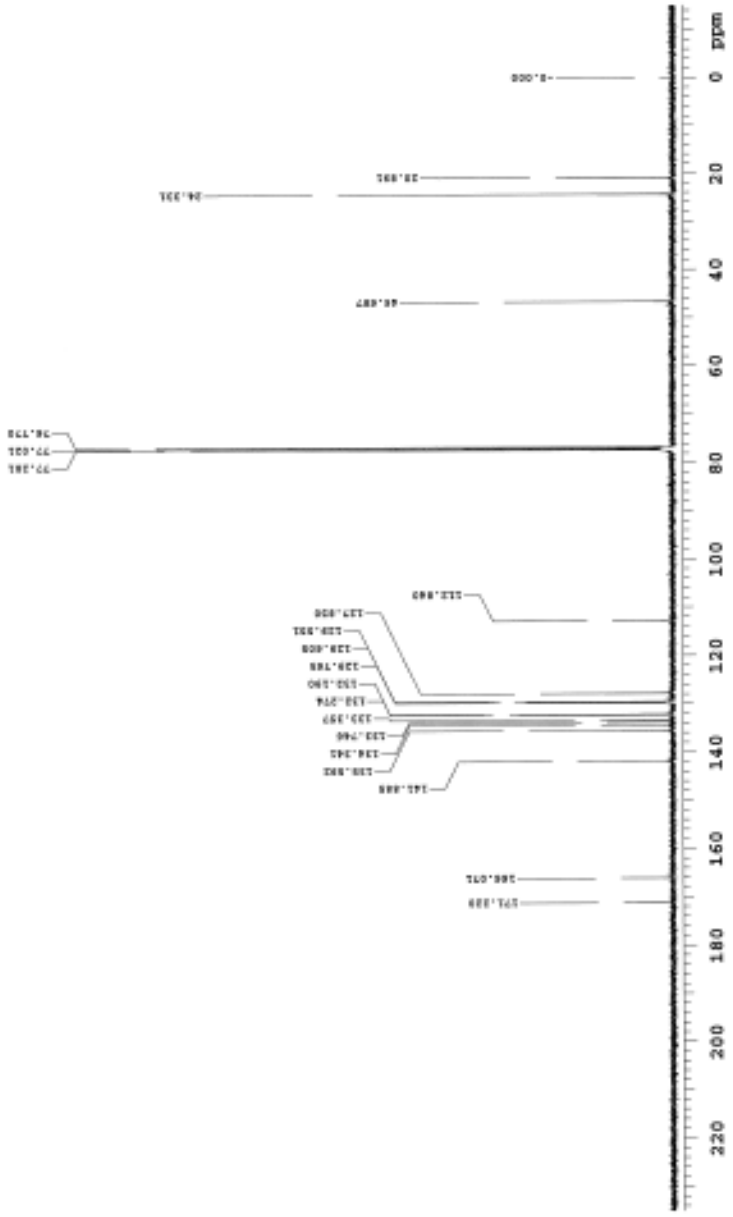
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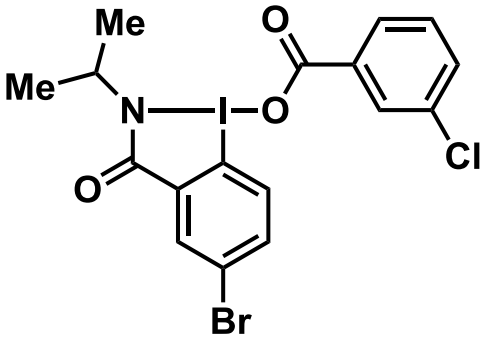
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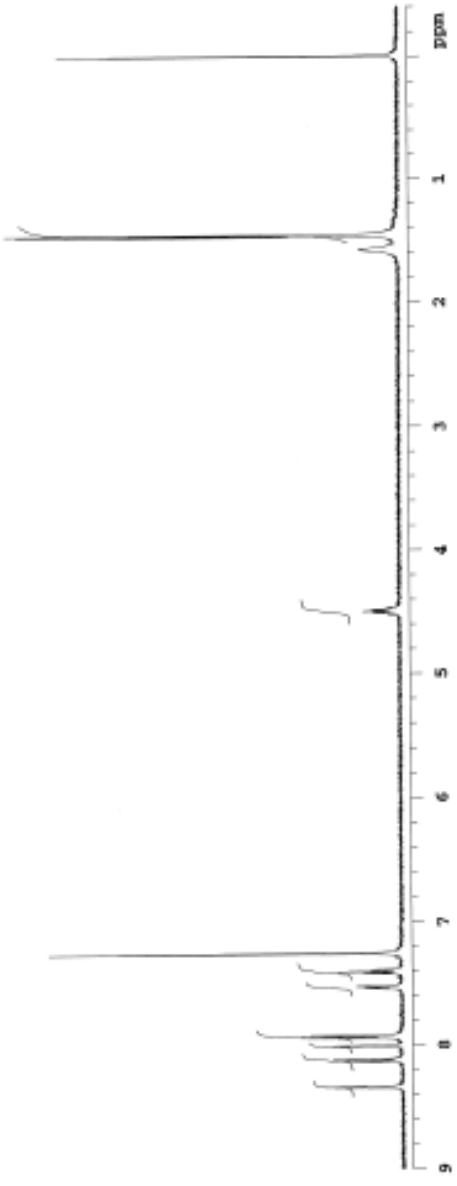
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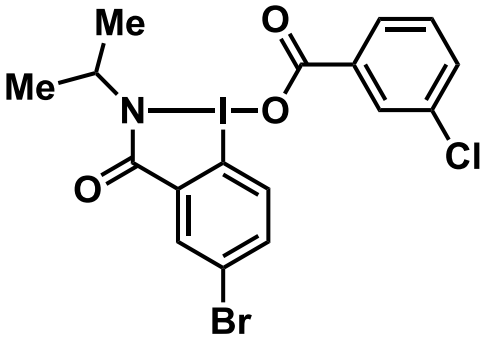
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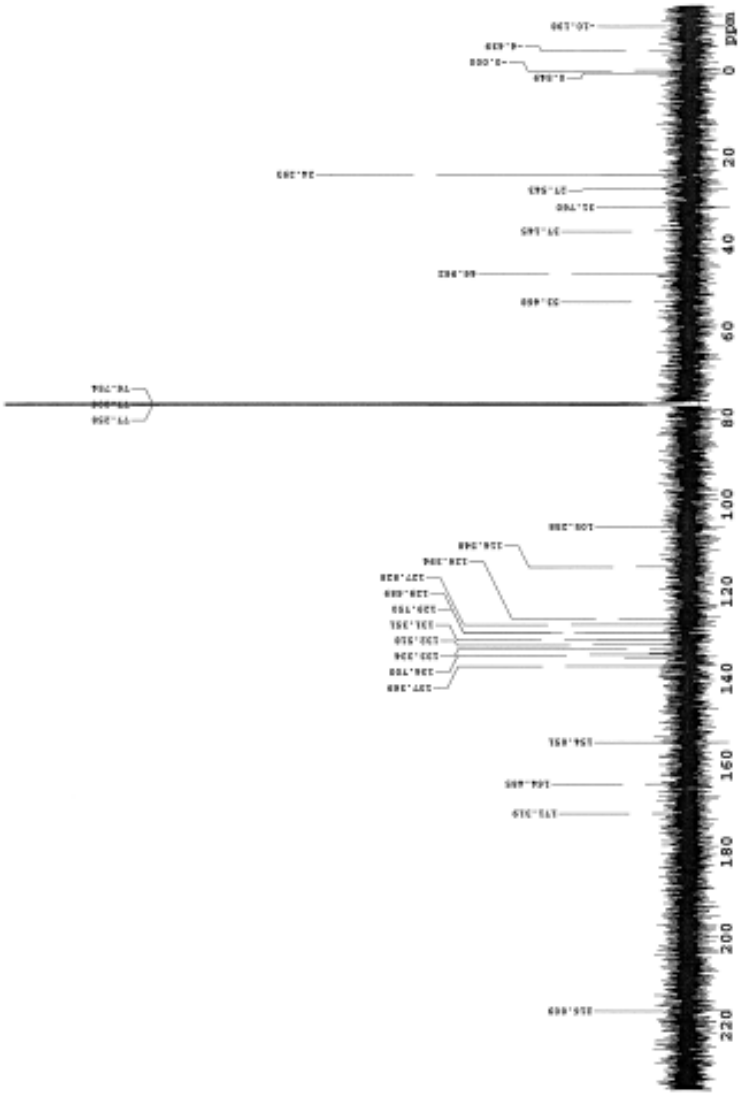
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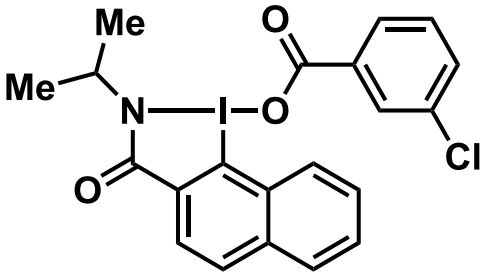
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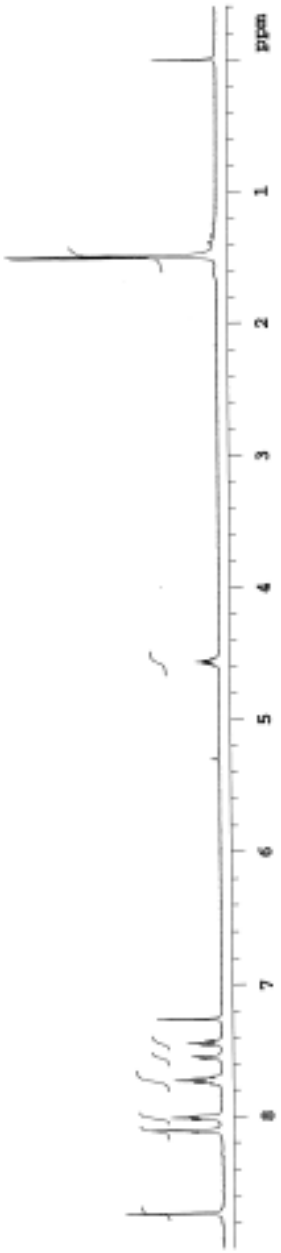
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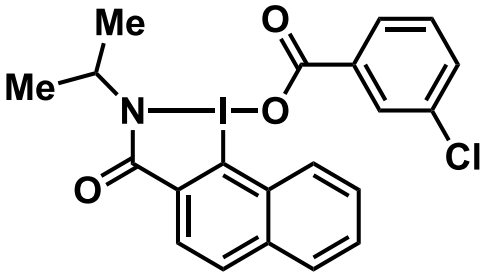
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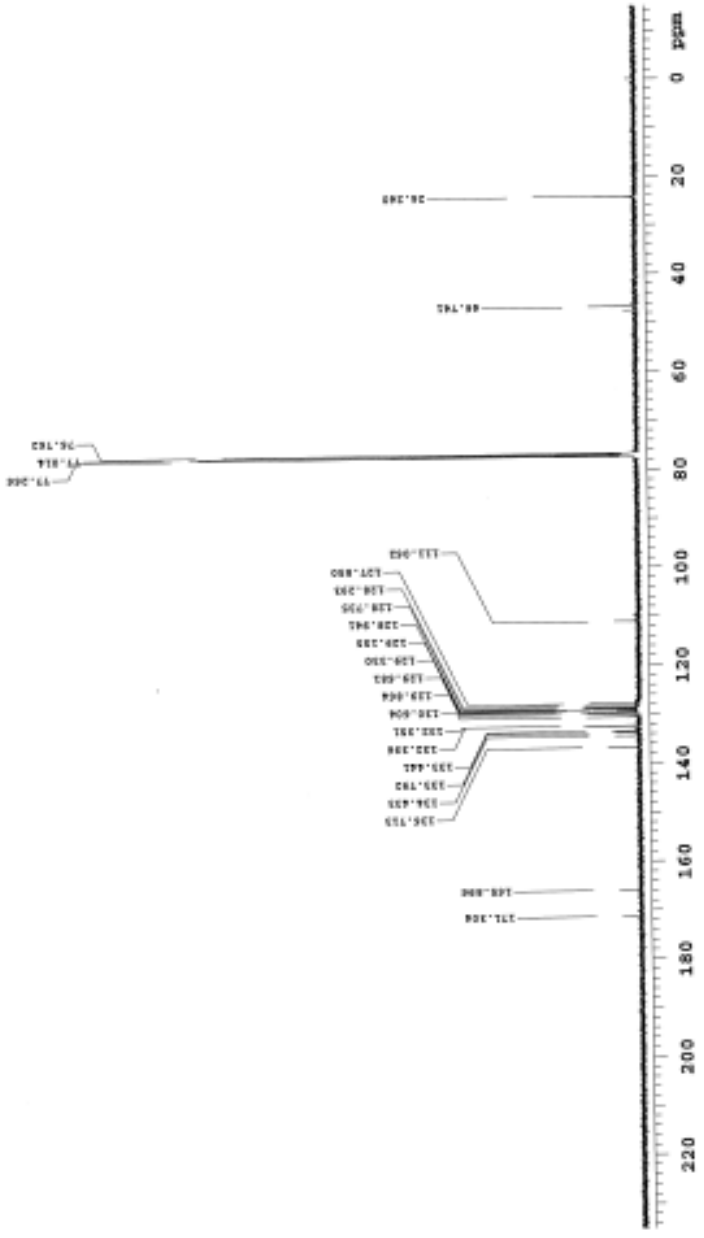
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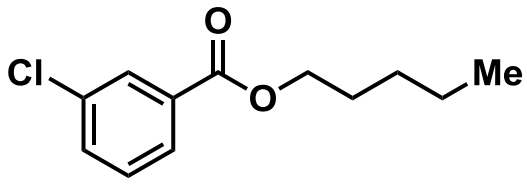
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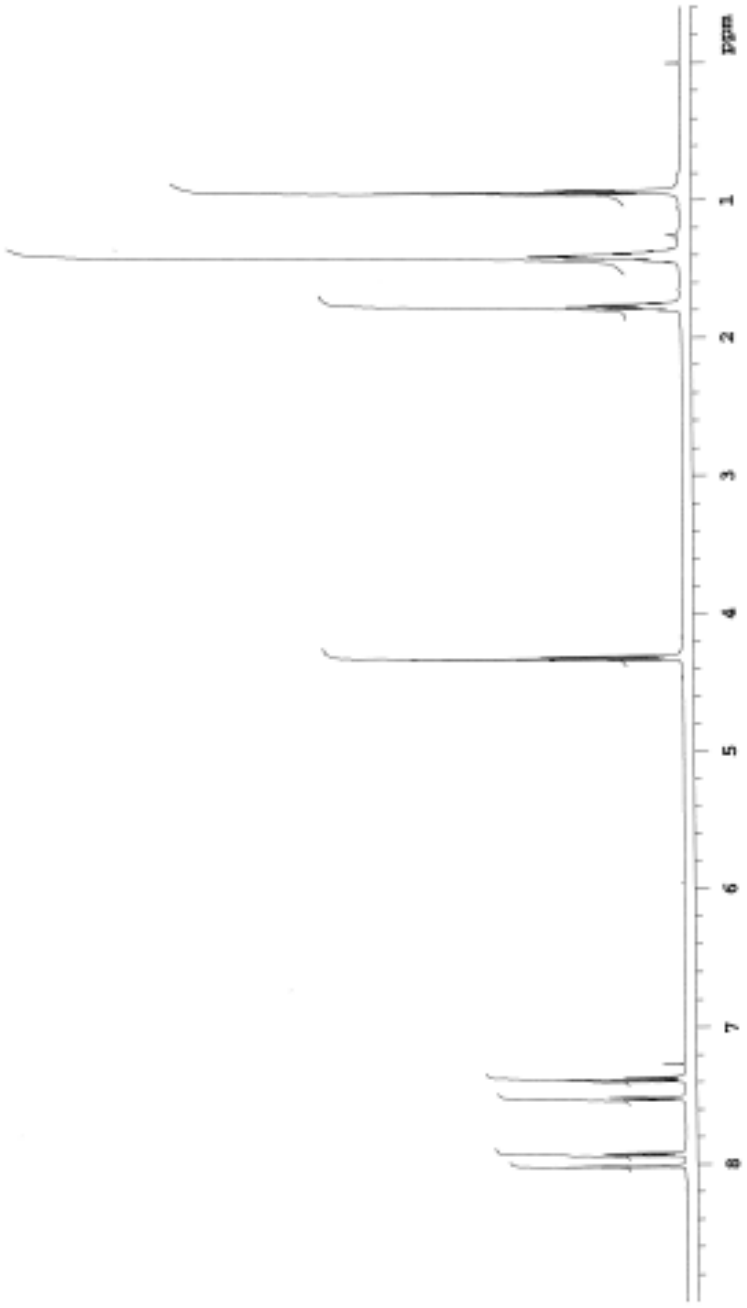
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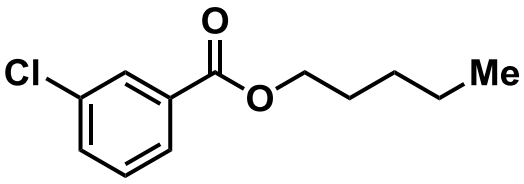
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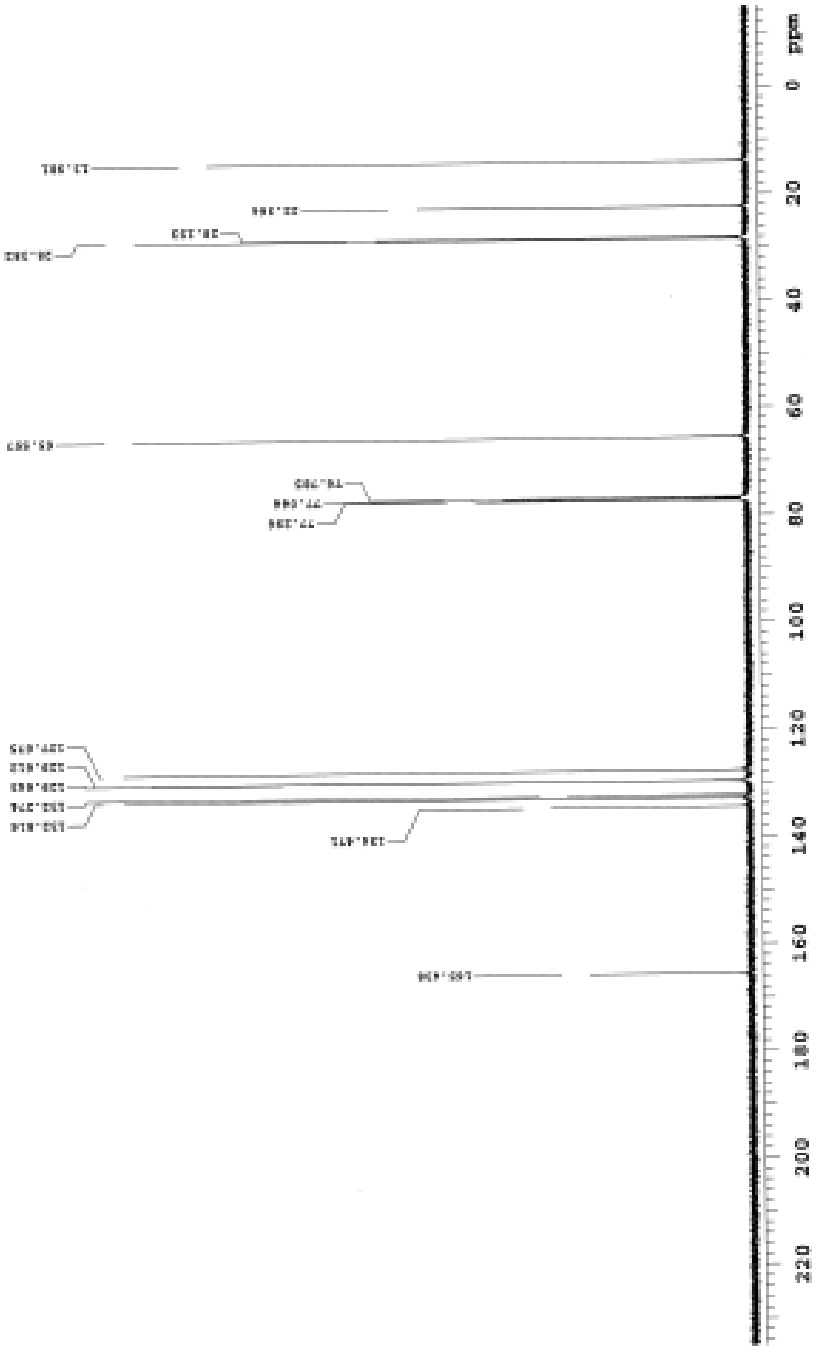
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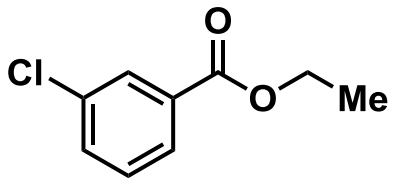
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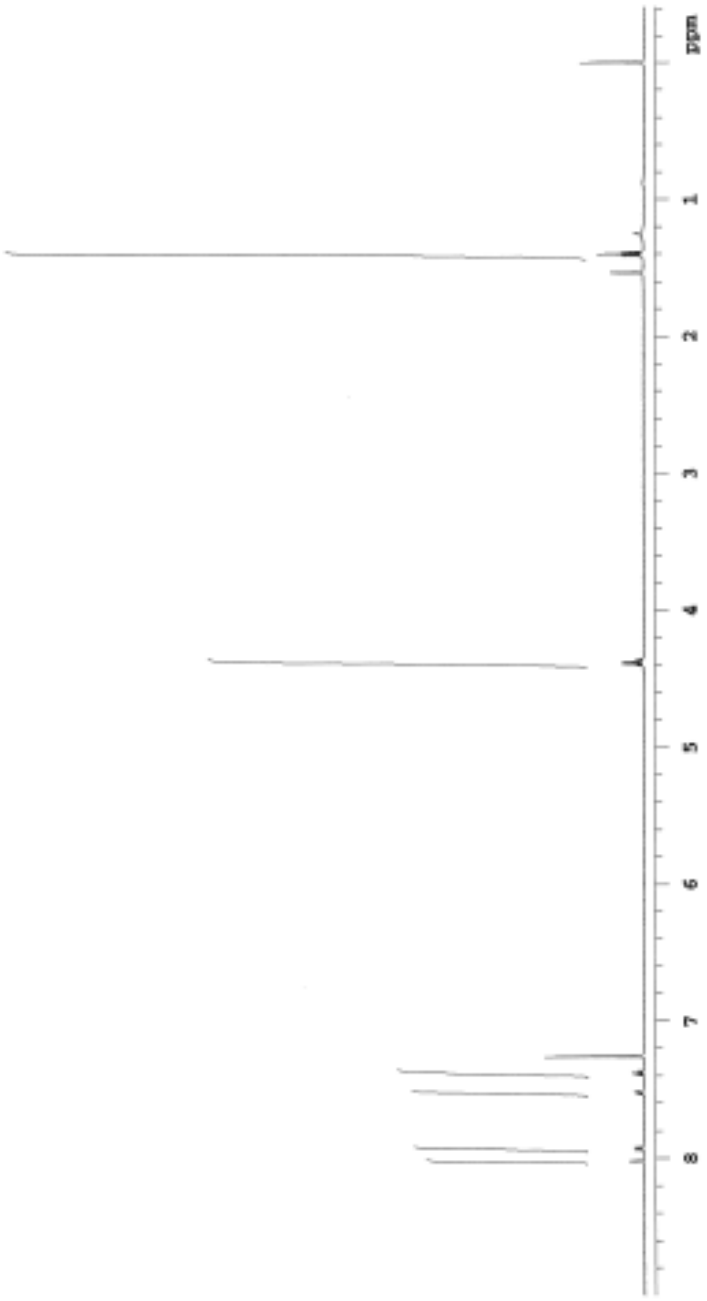
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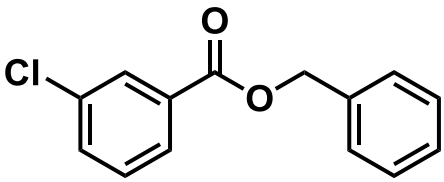
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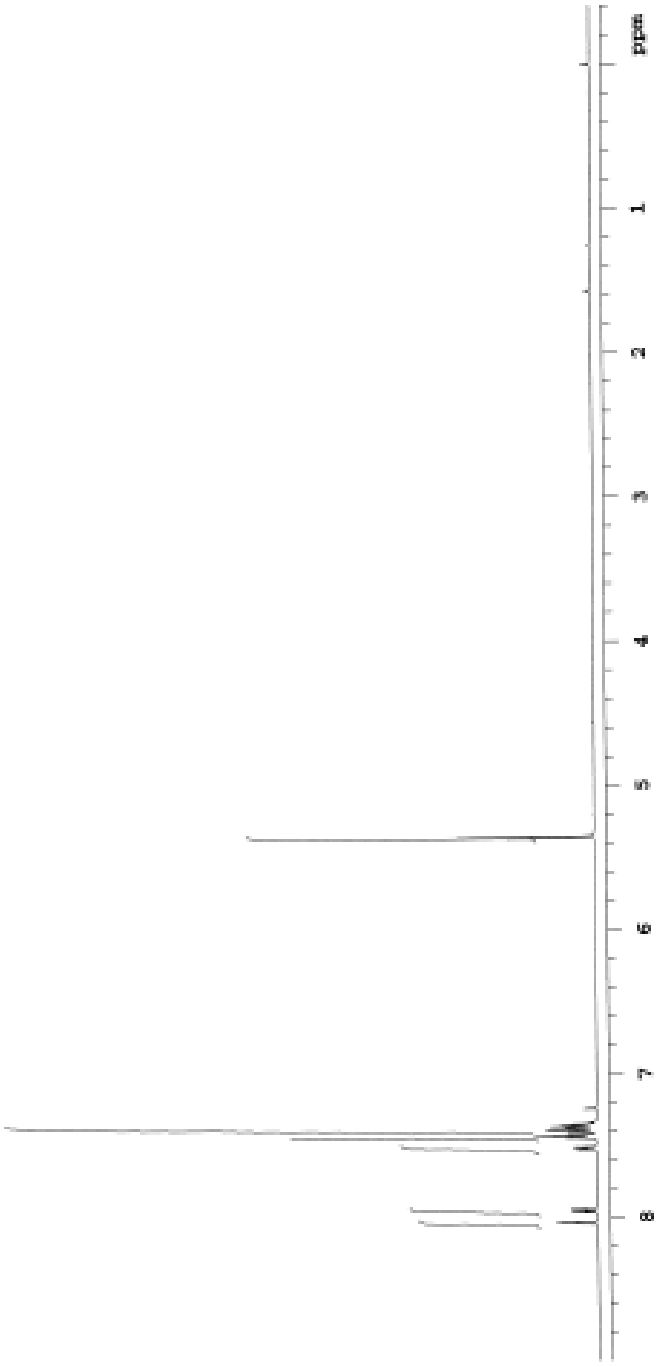
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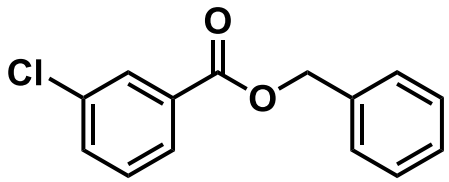
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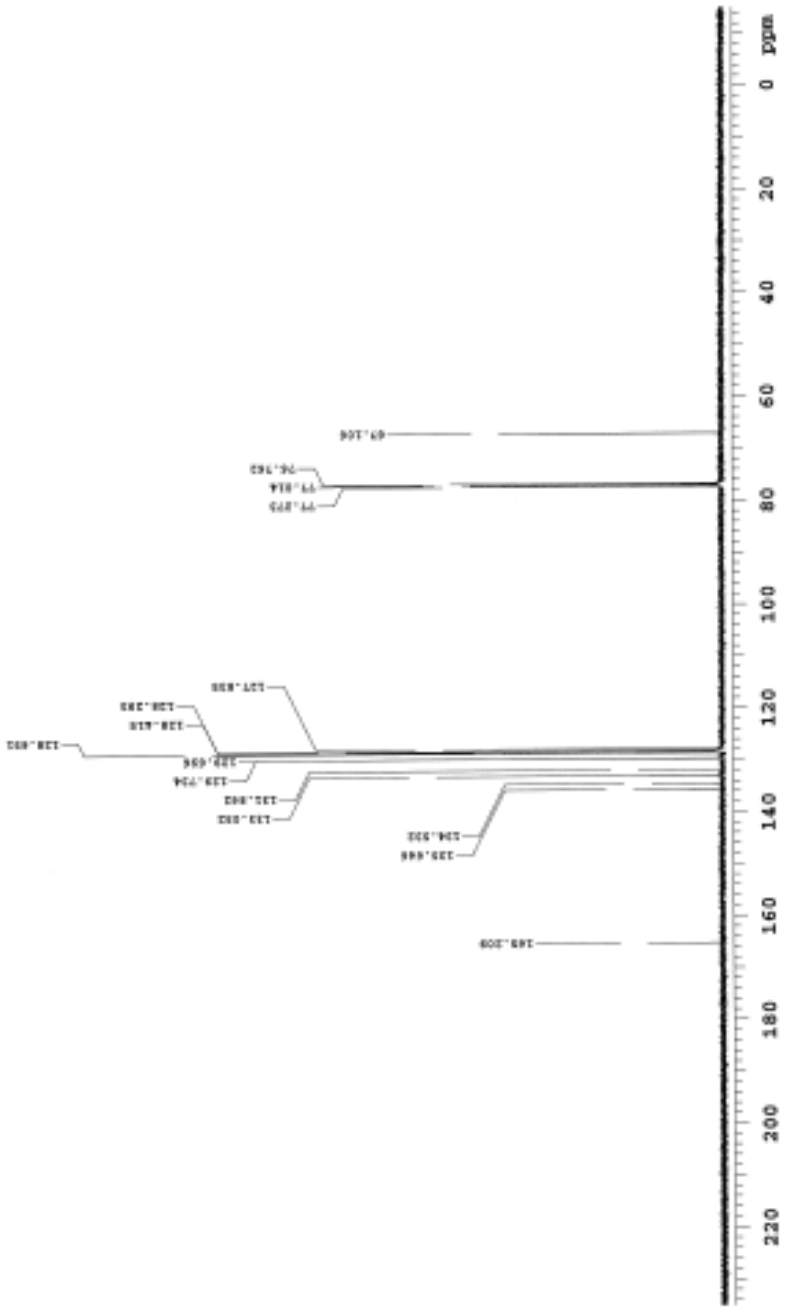
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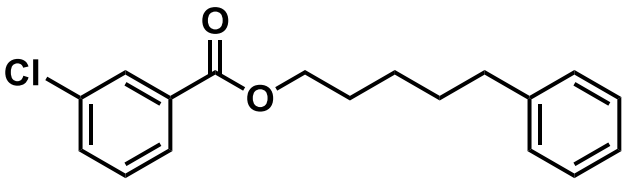
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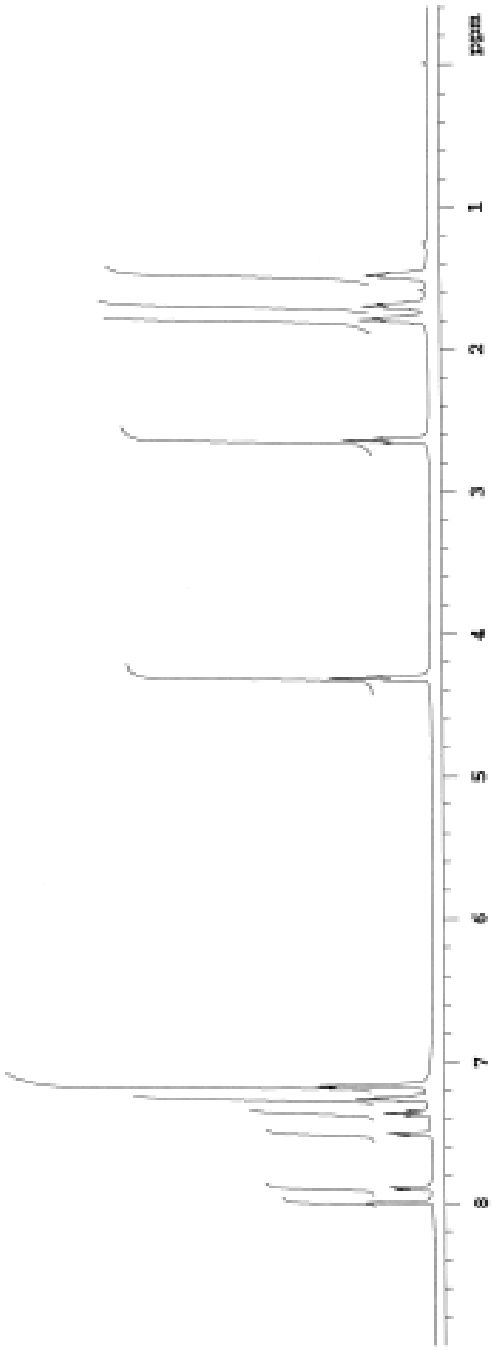
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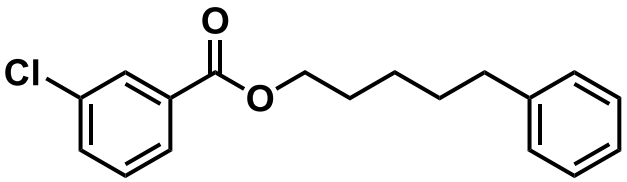
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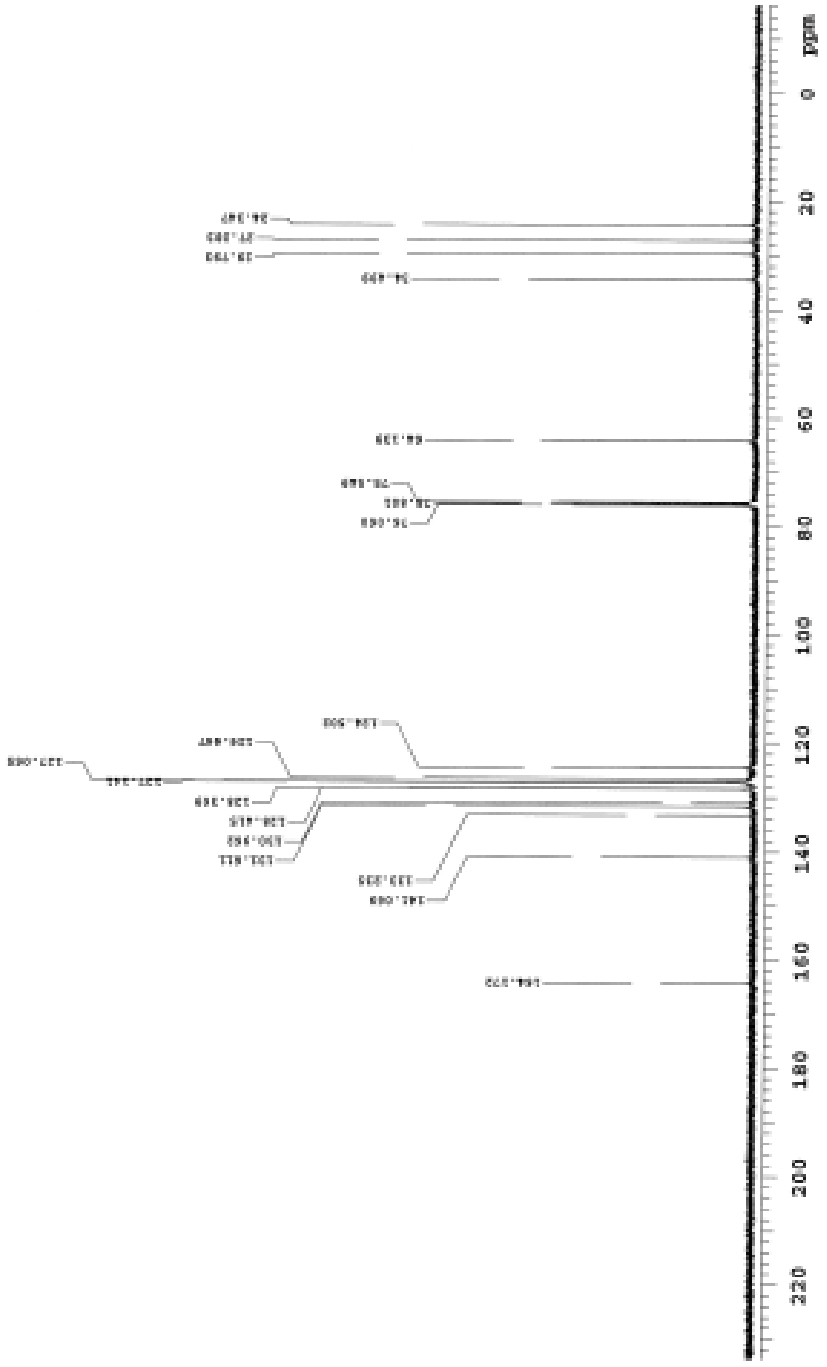
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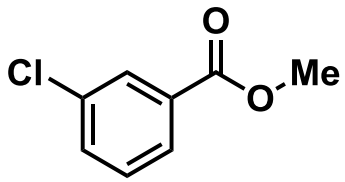
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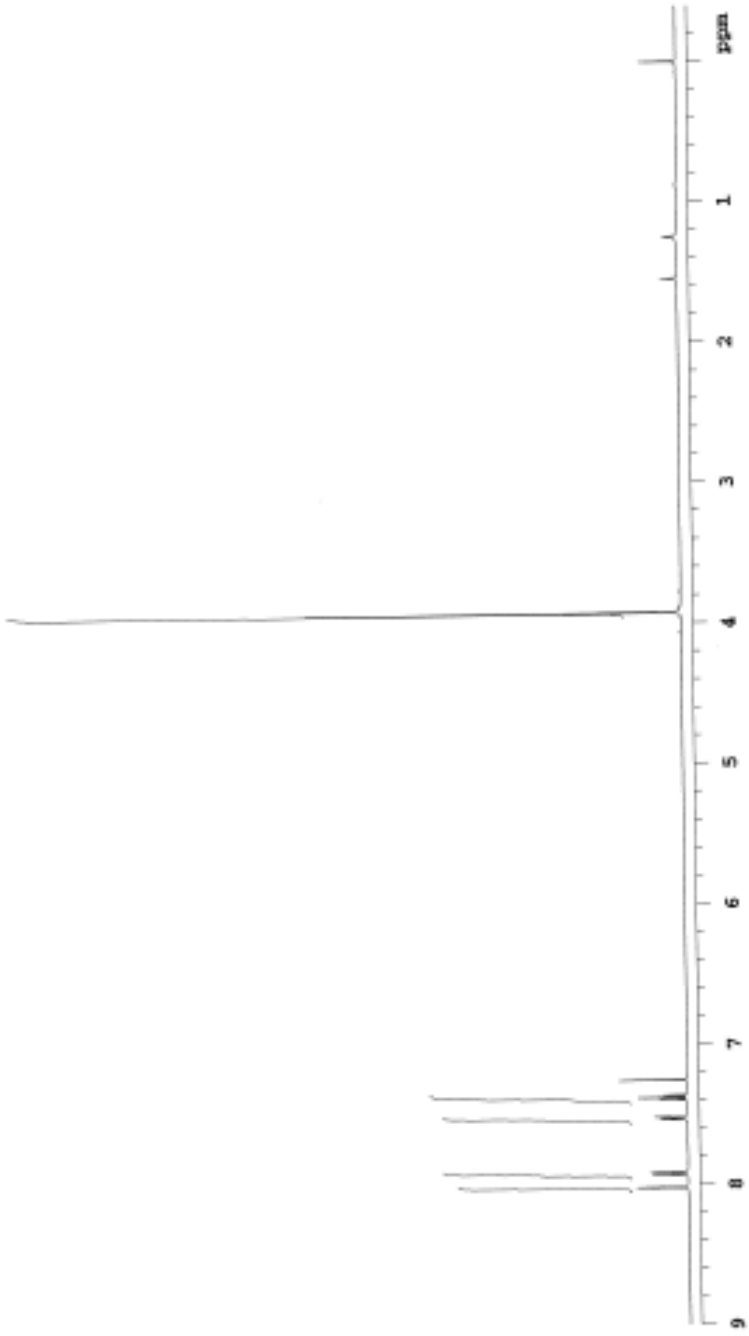
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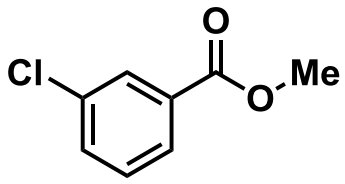
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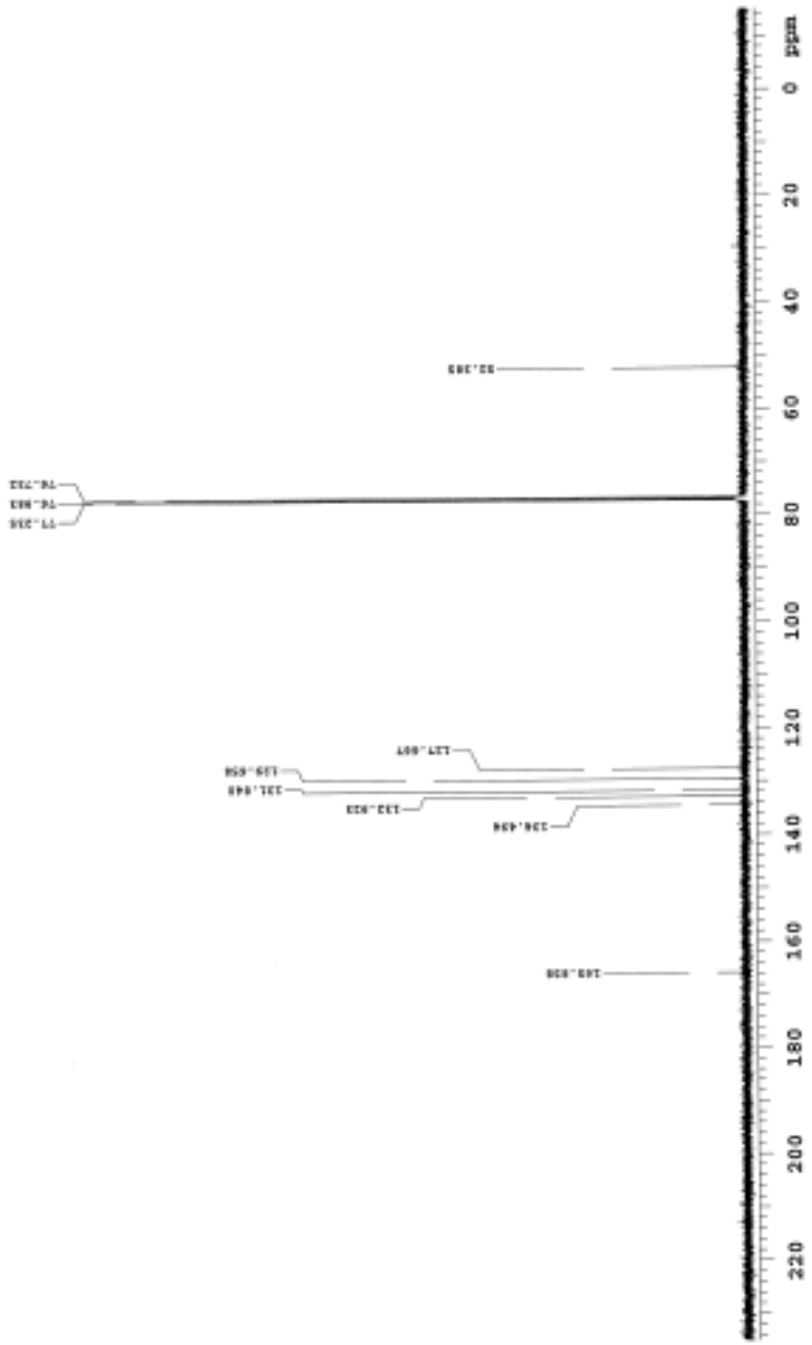
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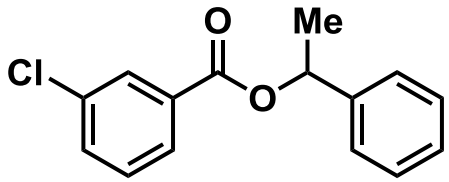
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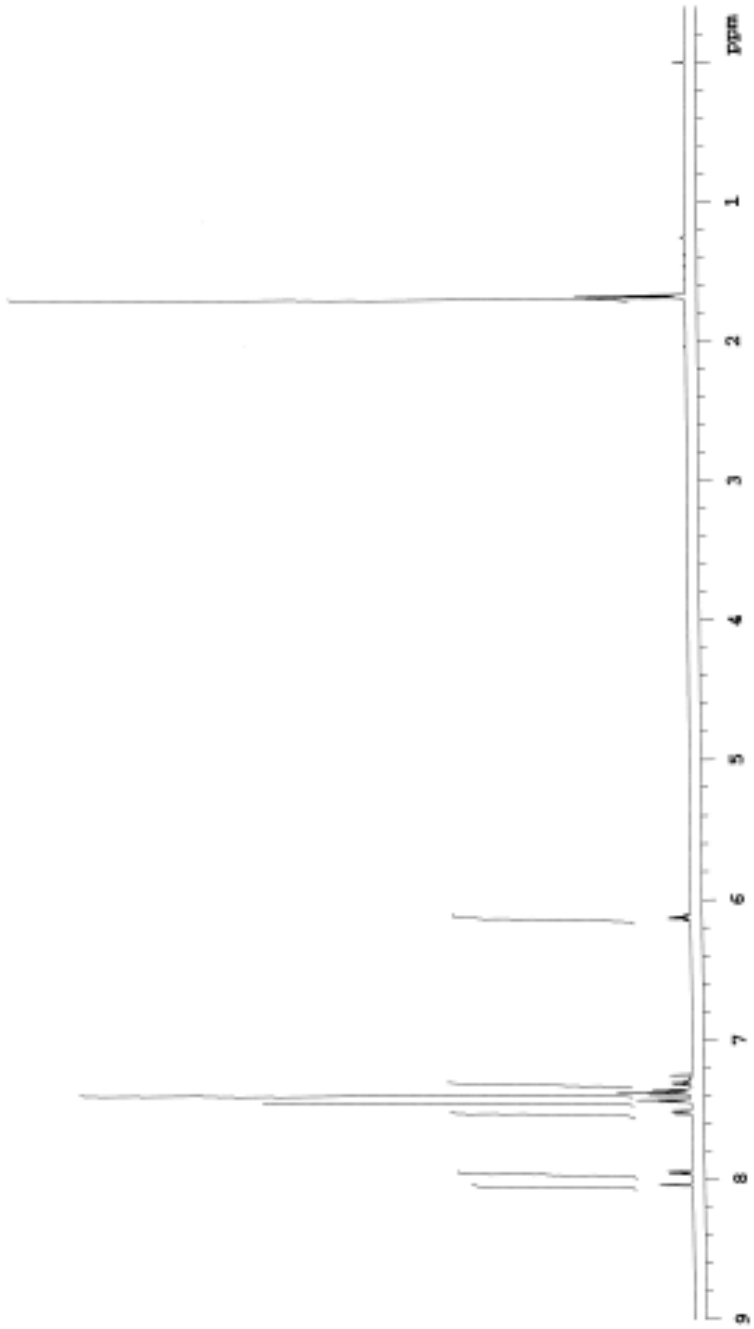
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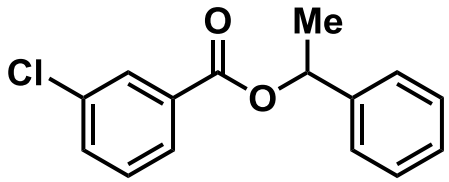
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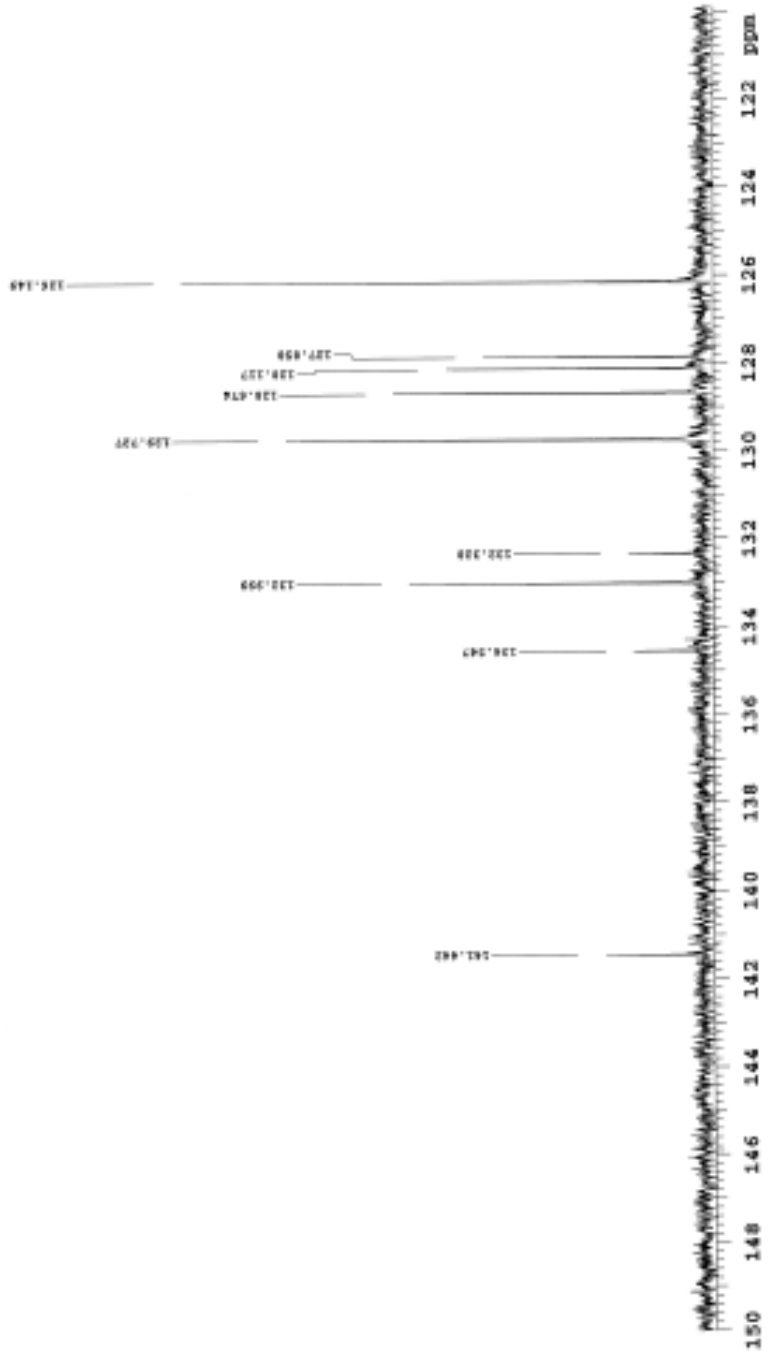
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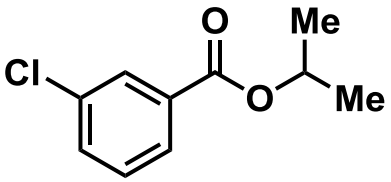
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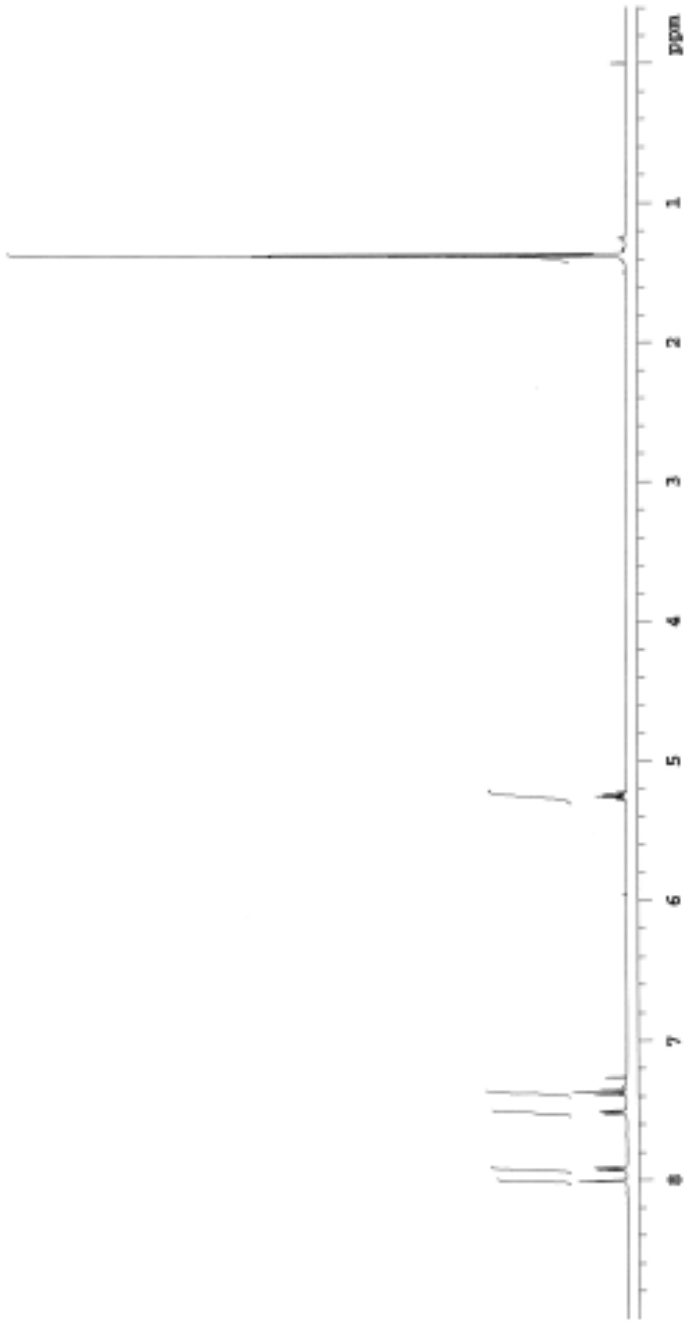
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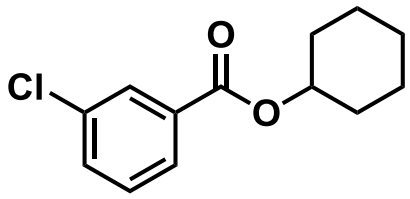
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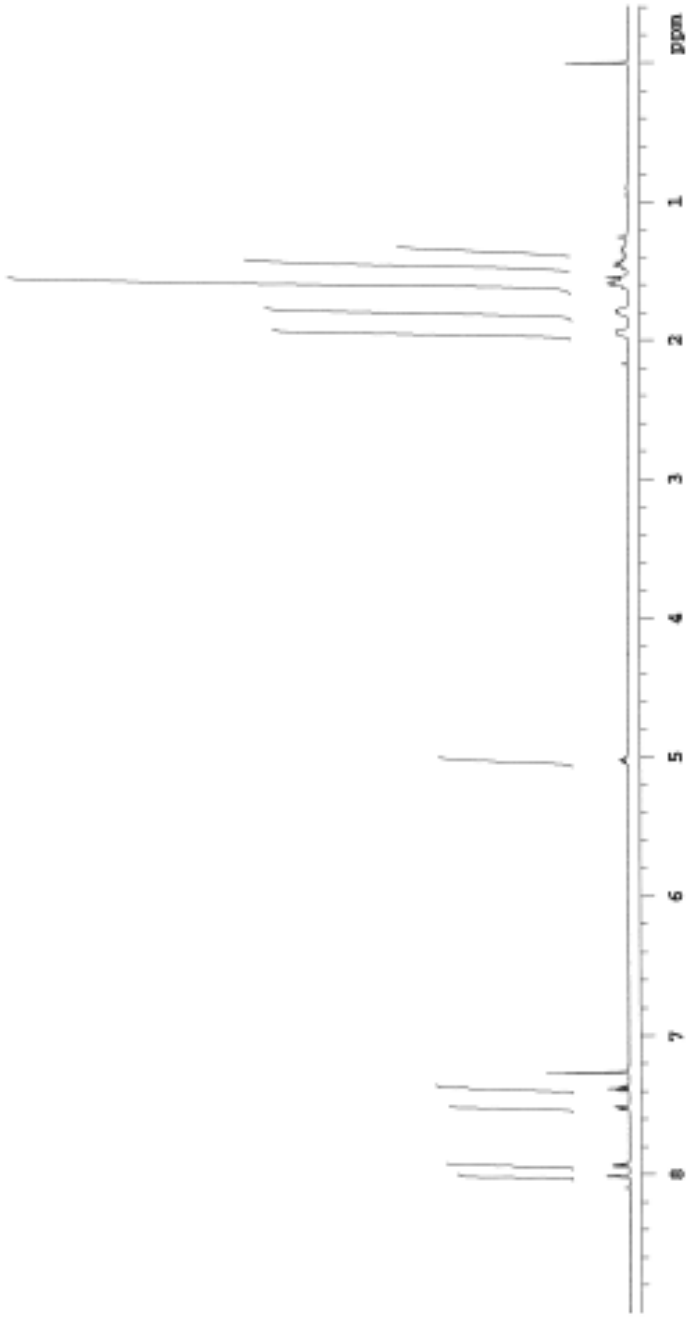
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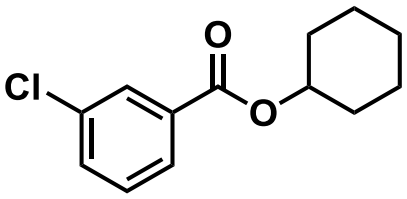
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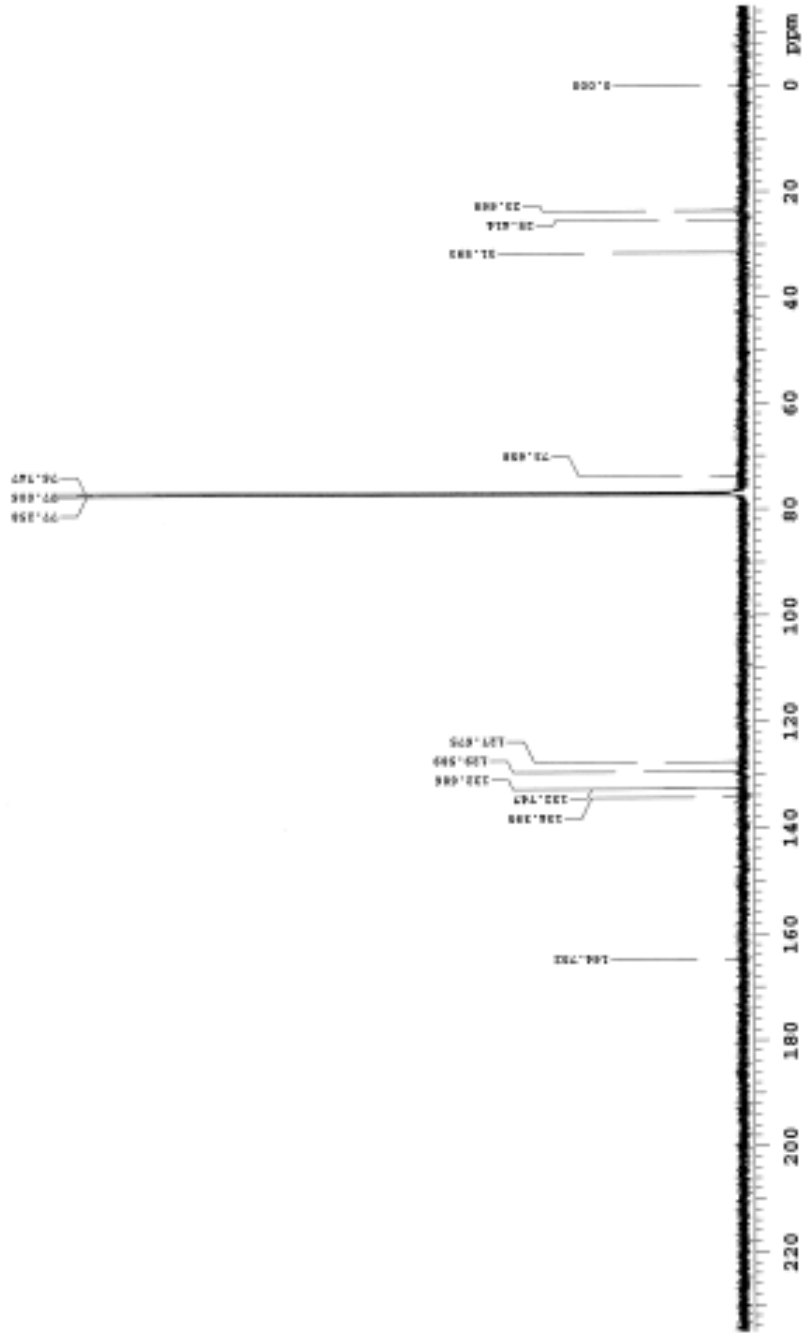
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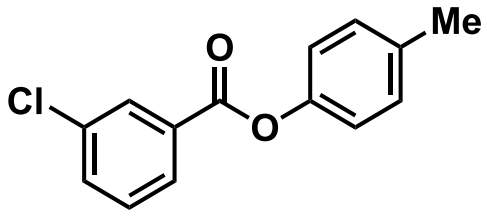
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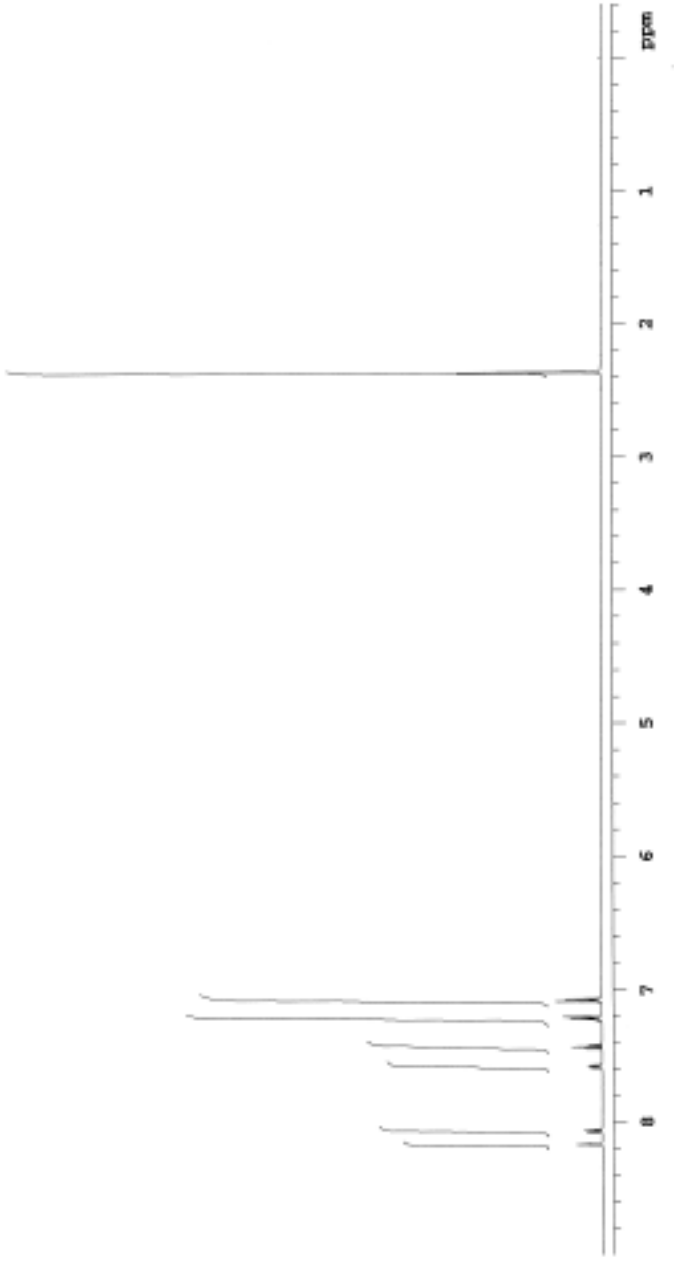
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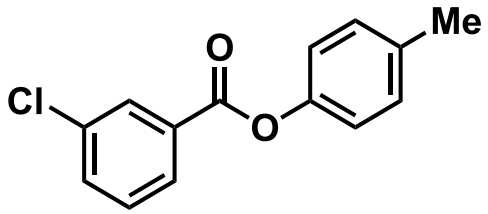
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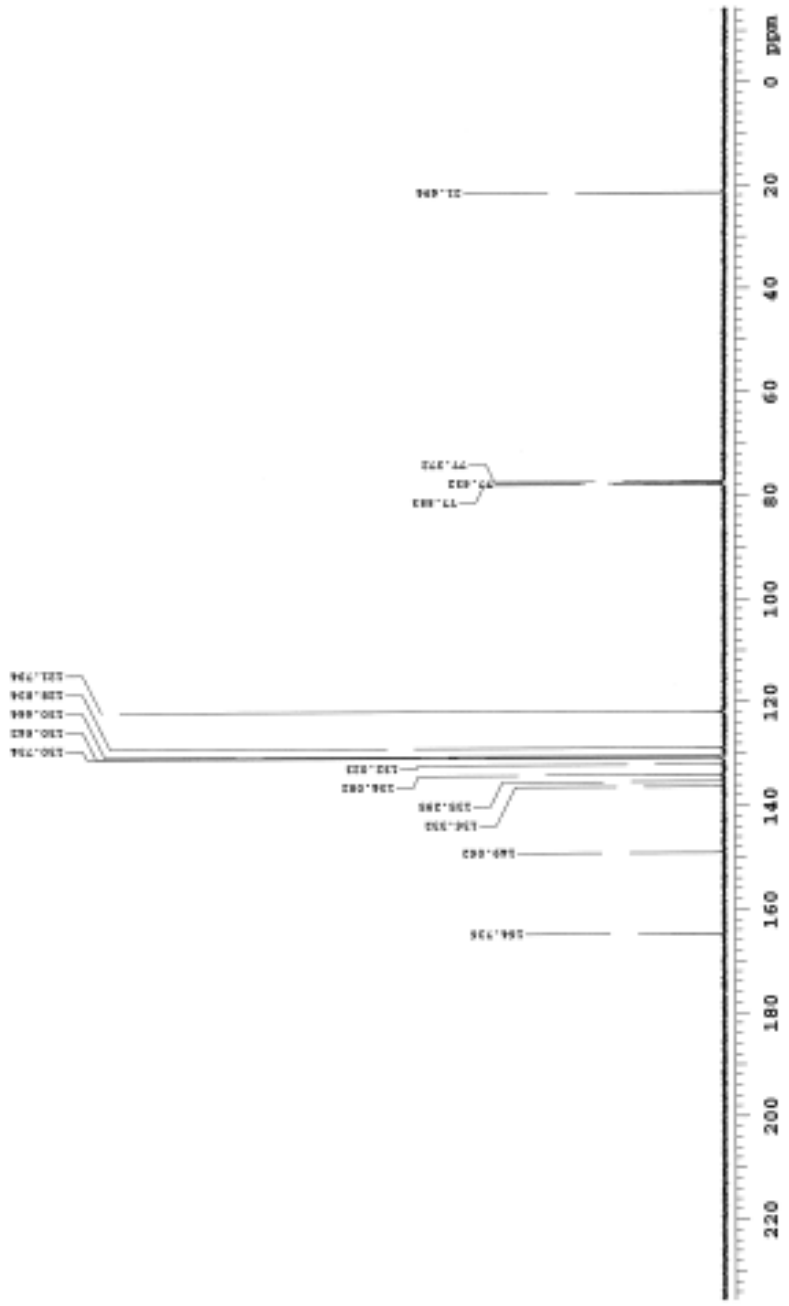
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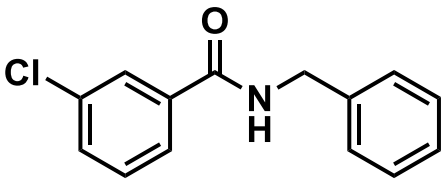
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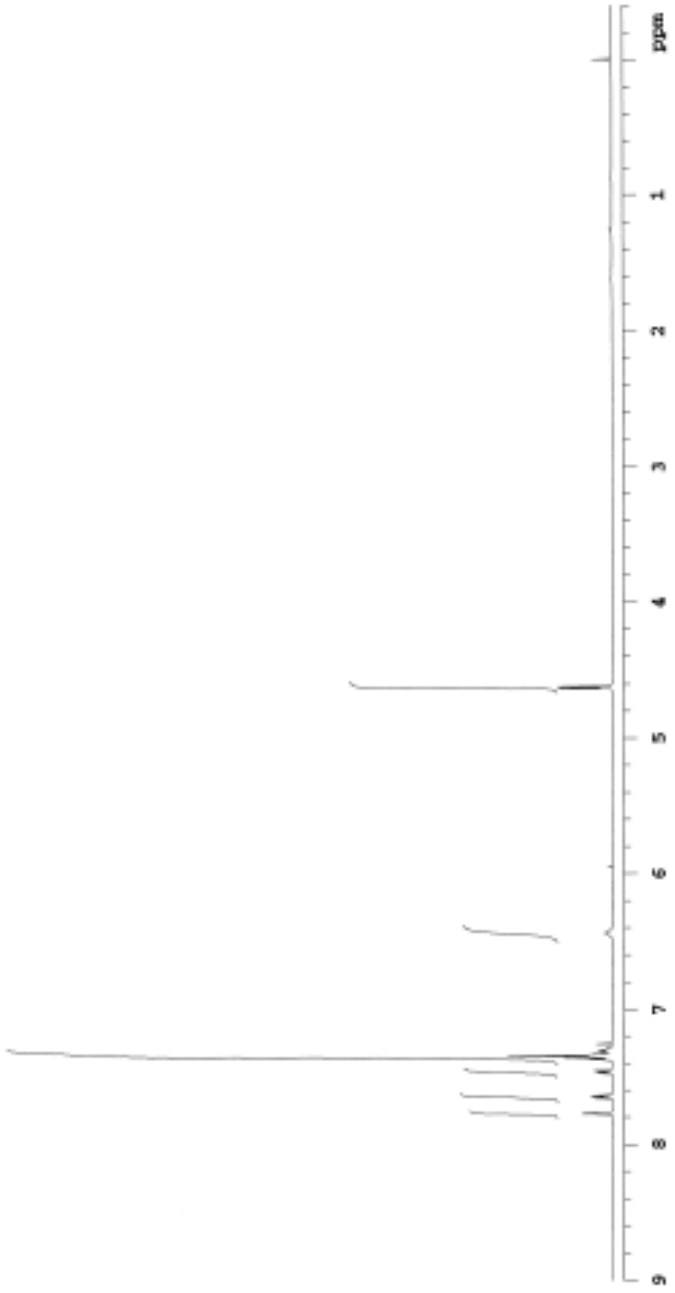
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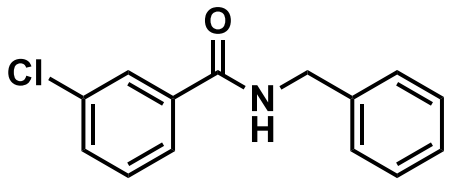
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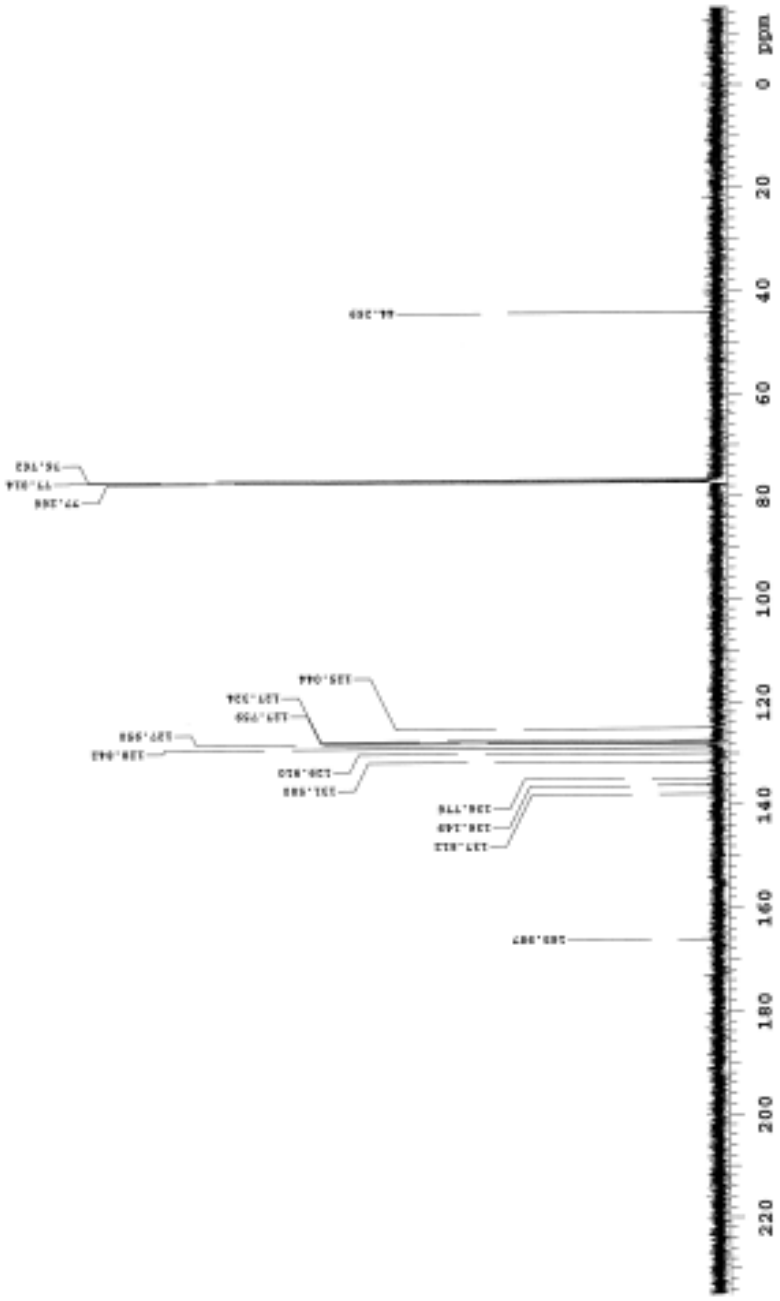
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